5 Iron physiology, iron overload, and the porphyrias

Elizabeta Nemeth and Carol Mathew

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The online version of this chapter contains educational multimedia components on the hormone erythroferrone and on the pathogenesis of porphyria.

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Off-label drug use: Off-label use of iron chelation therapy is discussed.

Introduction

Iron is vital for survival, but iron excess can be harmful, so iron balance must be tightly regulated. Essential functions of iron include oxygen transport and exchange, production of ATP, production of oxygen radicals as well as protection from oxidative damage, DNA synthesis and repair, cellular oxygen sensing, regulation of gene expression, amino acid and lipid metabolism, and many others. The ability of iron to accept and donate electrons allows it to shuttle between the ferrous (Fe^{2+}) and ferric (Fe^{3+}) oxidation states and is essential for its participation in a number of enzymatic reactions. Under physiologic states, iron is mostly bound to proteins and chaperones, but in conditions of iron overload, excess iron catalyzes the formation of free radical ions that may be harmful to cells. Causes of iron overload include repeated blood transfusions, the ineffective erythropoiesis of certain chronic anemias, and mutations in iron-regulatory genes that result in increased iron absorption. This chapter focuses on iron physiology in the normal host and in iron overload states, including hemochromatosis and transfusional iron overload in acquired anemias. Also discussed are the porphyrias as disorders of heme synthesis. Iron deficiency anemia is discussed with the underproduction anemias in Chapter 6.

Regulation of iron homeostasis

Body iron economy

Under normal conditions, dietary iron intake is usually 15 to 25 mg daily, of which only 5% to 10% (1 to 2 mg) is absorbed through the gastrointestinal (GI) tract (Figure 5-1). A similar amount of iron is lost daily by desquamation of GI epithelial cells. The average total body content of iron is 3 to 4 grams and may be lower in menstruating women. Approximately two-thirds of this iron is present in hemoglobin. Iron is stored in cells, predominantly macrophages of the spleen, bone marrow, and liver, but also in hepatocytes as ferritin or hemosiderin (partially denatured ferritin). At steady state, the serum ferritin concentration is a reasonably good reflection of total body iron stores. Total storage iron is approximately 1 g in men and 0.5 g in women. Additional iron is found as myoglobin in muscle and in cytochromes and other enzymes (~0.3 g).

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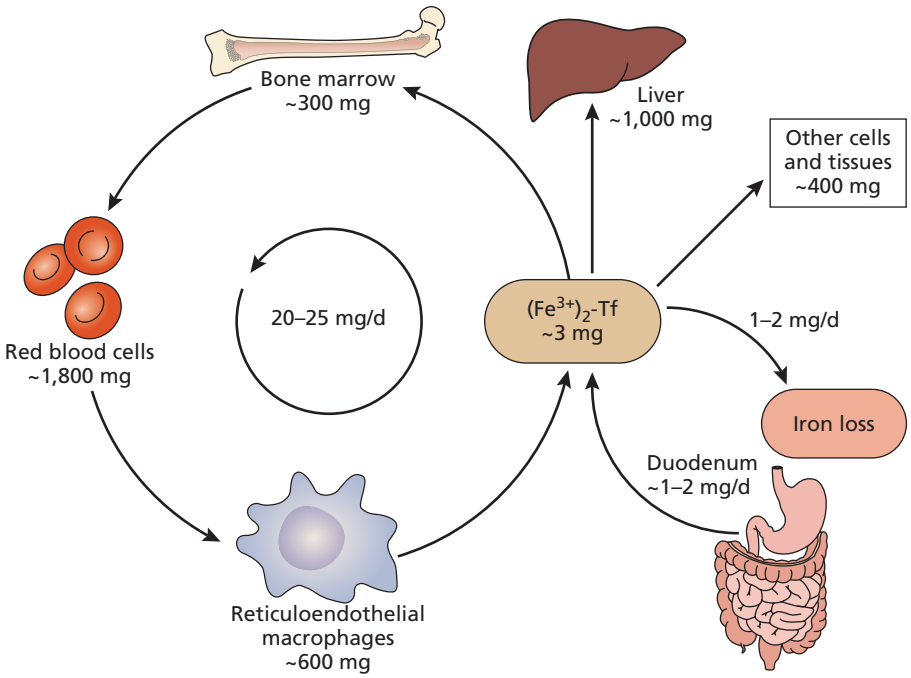

Figure 5-1 Body iron homeostasis. Plasma iron levels are maintained in a relatively narrow range (10 to 30 μM). Iron circulates in plasma bound to transferrin (Tf), which maintains iron in a soluble form, serves as a major route of entry for iron into cells (via the transferrin receptor TFR1), and limits the generation of toxic radicals. The homeostatic system responds to signals from pathways that consume iron (eg, erythropoiesis) and sends signals to the cells that supply iron to the blood stream. Iron is released into the circulation from duodenal enterocytes, which absorb 1 to 2 mg of dietary iron per day, and from macrophages, which internally recycle 20 to 25 mg of iron per day from senescent erythrocytes. Although the body regulates processes of iron absorption, storage, and recycling, there is no process for excreting excess iron. Redrawn from Hentze MW et al, *Cell*. 2004;117:285-297 (© 2004), with permission from Elsevier.

Iron is released into the circulation through the iron transporter ferroportin, expressed on the basolateral surface of iron-absorbing enterocytes, on iron-recycling macrophages, and on hepatocytes. Ferroportin activity and levels are controlled by the hormone hepcidin: hepcidin binding occludes ferroportin and triggers its degradation, decreasing iron transport into plasma. Hepcidin production in the liver is itself regulated by iron: When circulating iron is low, hepcidin levels are low, allowing GI iron absorption to increase and iron stores to be mobilized. When iron is plentiful, hepcidin levels increase and block iron absorption and release from stores.

In the circulation, iron is transported bound to transferrin and is taken up into cells via the transferrin receptor. Developing red blood cells (RBCs) in the bone marrow utilize most of the daily circulating iron. The iron-transferrin compartment is very small (~3 mg), but it has a high turnover rate so that it transports ~25 mg of iron daily. Under normal conditions, only around one-third of plasma transferrin is saturated with iron (reference ranges vary based on the clinical laboratory but are generally around 20% to 50%).

Iron balance is regulated such that the amount absorbed equals the amount lost. Importantly, there is no physiologically regulated pathway for excretion of excess iron in iron overload, and the regulation of total body iron is achieved by regulating the rate of iron absorption. Over the past 20 years, considerable progress has been made concerning the molecular mechanisms underlying the absorption, transport, utilization, and storage of iron. The key proteins discussed are listed in Table 5-1.

Table 5-1 Major proteins involved in iron homeostasis

Protein	Location	Function	Comments
DCYTB	Duodenal enterocytes, apical surface	Absorption of nonheme iron	Reduces dietary Fe^{3+} to Fe^{2+}, which is then transported by DMT1
DMT1	Duodenal enterocytes, apical surface	Absorption of nonheme iron	Transports Fe^{2+} across the luminal cell surface
Sodium-hydrogen antiporter 3 (NHE3)	Duodenal enterocytes, apical surface	Absorption of nonheme iron	Generates the H(+) gradient that drives DMT1-mediated iron uptake
FPN1 (SLC40A1)	Ubiquitous expression but particularly high on: duodenal basolateral surface; hepatocyte cell surface; macrophage cell surface	Iron transport into plasma	Exports iron out of enterocytes, macrophages, and hepatocytes into the plasma

Table continues on next page

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Table 5-1 Major proteins involved in iron homeostasis *(continued)*

Protein	Location	Function	Comments
HEPH	Duodenal enterocytes, basolateral membrane	Iron absorption	Ferroxidase; oxidizes Fe^{2+} to Fe^{3+}; facilitates iron export via ferroportin into the circulation
Ceruloplasmin (CP)	Plasma and macrophages, liver, central nervous system	Mobilization of stored iron	Ferroxidase; enhances the export activity of ferroportin and loading of iron onto transferrin
TF	Plasma	Iron transport in the circulation	Apotransferrin, no bound iron; holotransferrin, $2Fe^{3+}$ bound
TFR1	Cell surface of most cells	Cellular iron uptake	Particularly high expression on erythroid precursors
Ferritin	Intracellular and circulating forms	Iron storage (intracellular form)	Function of the circulating form unknown
IRP-1 and -2	Cytoplasm	Regulate production of proteins involved in cellular iron uptake, storage, and export	Bind to IREs on mRNA; stabilize mRNAs with 3′ IRE (TFR1, DMT1); decrease translation of mRNAs with 5′ IREs (ferritin, ferroportin, HIF-2α ALAS2)
Hepcidin (HAMP)	Hormone produced mainly by the liver	Regulates plasma iron by controlling iron absorption and release from stores	Occludes ferroportin and causes its degradation
ERFE	Hormone produced by erythroid precursors	Regulates hepcidin in response to erythropoietic stimulation	Suppresses hepcidin, allowing iron absorption and mobilization of stored iron
HFE	Ubiquitous expression, prevalent function in hepatocyte	Regulates hepcidin in response to iron stimulation	A protein mutated in most cases of hereditary hemochromatosis
HJV	Hepatocyte cell surface	Regulates hepcidin in response to iron stimulation	A BMP coreceptor
TFR2	Hepatocyte cell surface; erythroid precursors	Regulates hepcidin in response to iron stimulation; modulates EPOR on erythroid precursors	Holotransferrin sensor
BMPs	Growth factors	Regulate hepcidin baseline and response to iron stimulation	Produced by the liver sinusoidal endothelial cells
BMP receptors (ALK2, ALK3; ACTRIIA and BMPR2)	Hepatocyte cell surface	Regulate hepcidin baseline and response to iron stimulation	Activate SMAD 1/5/8 pathway to increase hepcidin transcription
SMAD proteins	Intracellular signal transduction and transcription factors	Regulate hepcidin baseline and response to iron stimulation	Phospho-SMAD 1/5/8 complexing with SMAD 4 promotes hepcidin gene transcription
TMPRSS6	Hepatocyte cell membrane	Regulates hepcidin response to iron deficiency	Serine protease; decreases BMP signaling by binding and inhibiting HJV and other components of the BMP pathway
IL-6, IL-6 receptor	Cytokine and its receptor	Regulate hepcidin in response to inflammation	Increase hepcidin transcription by activating the JAK/STAT pathway
HIF2α	Intracellular transcription factors	Regulates iron absorption	Activates duodenal transcription of ferroportin, DMT1, and Dcytb; may contribute to iron overload in ineffective erythropoiesis; regulates erythropoietin production in the kidneys

Intestinal iron absorption

Iron is found in food as inorganic iron or as heme (iron complexed to protoporphyrin IX). The typical diet consists of 90% inorganic and 10% heme iron, though diets in the industrial world can contain up to 50% heme iron from iron-rich meats. The bioavailability of inorganic but not heme iron is influenced by multiple factors, such as other dietary constituents; take, for example, ascorbic acid (enhances bioavailability) and phytates and polyphenols in cereals and plants (inhibit bioavailability). The rate of iron absorption is influenced by several factors, including body iron stores, the degree of erythropoietic activity, and the presence of inflammation. Iron absorption increases when stores are low or when erythropoietic activity increases, such as during anemia or hypoxemia, and this is at least in part regulated by hepcidin. Conversely, the physiologically appropriate response to iron overload is downregulation of intestinal

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iron absorption; this downregulation fails in patients with hereditary hemochromatosis or anemias with ineffective erythropoiesis.

Iron is absorbed in the intestine via 2 pathways (Figure 5-2): one for inorganic iron and the other for heme-bound iron. Little is known about heme absorption. Nonheme iron in the diet is largely in the form of ferric oxyhydroxides (Fe^{3+}), but the intestinal epithelial cell apical iron importer, divalent metal transporter 1 (DMT1 or SLC11A2), transports only ferrous iron (Fe^{2+}). Iron must therefore be reduced to be absorbed, and this is facilitated by a ferrireductase duodenal cytochrome B (Dcytb). Once transported across the apical border of the enterocyte, iron may be stored within the cell in ferritin. Eventually, the cell senesces and sloughs off into the feces, and stored enterocyte iron is lost from the body. Alternatively, enterocyte iron may be transported across the basolateral membrane into the portal circulation via ferroportin. Ferroportin (FPN) 1 (gene *SLC40A1*) is the only known iron exporter in mammals and, like DMT1, transports only ferrous iron. Once ferrous iron is transported across the basolateral membrane by ferroportin, it is oxidized to ferric iron by hephaestin and is loaded onto plasma transferrin.

As discussed previously, intestinal iron absorption is regulated by the hepcidin-ferroportin interaction. During iron deficiency and anemia, intestinal iron absorption is further increased through the activity of the intestinal hypoxia-inducible factor 2α (HIF2α). HIF2α promotes transcription of ferroportin, DMT1, and Dcytb, leading to the coordinated increase in apical and basolateral transport of iron. Activation of this pathway may also contribute to the development of iron overload in anemias with ineffective erythropoiesis.

Cellular iron uptake, storage, and recycling

Each molecule of transferrin (TF) can bind up to 2 ferric (Fe^{3+}) iron atoms. The ratio of monoferric and diferric transferrin in circulation varies depending on the plasma iron concentrations, but diferric transferrin has much greater affinity for transferrin receptor 1 (TFR1) and is the primary source of iron for cells under physiologic conditions. When iron-transferrin binds to the TFR1 on cell surface, the complex is internalized via receptor-mediated endocytosis; once in endosomes, acidification releases iron from the TF-TFR1 complex, and iron is transported into the cytoplasm by DMT1. Apo-TF

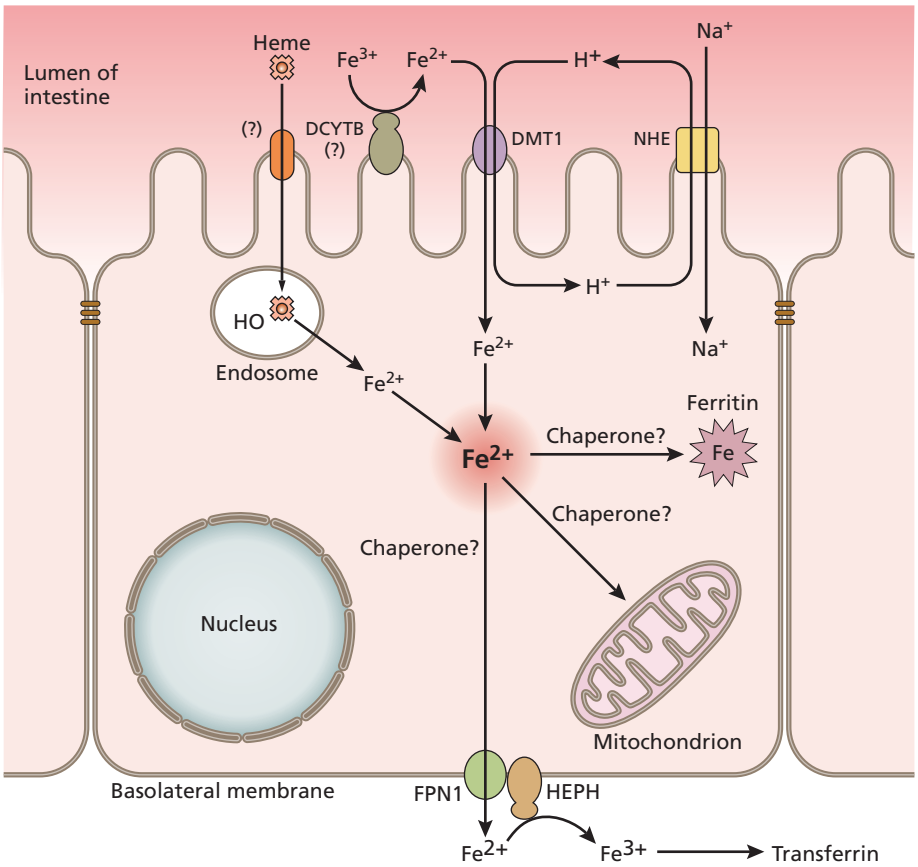

Figure 5-2 Intestinal iron absorption. The details of heme iron transport are not yet understood but likely involve endocytosis of heme followed by iron extraction from heme by heme oxygenase (HO). Nonheme iron in the diet is predominantly in the ferric from and must be reduced by a ferrireductase (eg, DCYTB). Ferrous iron is subsequently transported into cells via DMT1. The proton gradient needed for DMT1 activity is maintained by sodium-hydrogen antiporter 3 (NHE-3). Iron is exported out of enterocyte via FPN1 on the basolateral surface of the cell. The export of ferrous iron is coupled with iron oxidation via hephaestin (HEPH), and ferric iron then binds to transferrin in plasma. Modified from Gulec S et al, *Am J Physiol Gastrointest Liver Physiol*. 2014;307(4):G397-G409, with permission.

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and TFR1 are recycled to the cell surface. Regulation of the synthesis of multiple proteins involved in cellular iron homeostasis, including TFR1, DMT1, FPN1, and ferritin, is controlled at a posttranscriptional level by altering either mRNA stability or translation. The mRNAs of these proteins contain iron response elements (IREs), conserved nucleotide sequences with a stem-loop structure that binds iron-regulatory protein (IRP)-1 and IRP-2. The mRNAs for ferritin and FPN1 have IREs in the 5′-untranslated region (UTR), and the mRNAa for the TFR1 and DMT1 have IREs in the 3′-UTR. When a cell is iron deficient, IRPs bind to IREs. Binding to the 3′-IREs stabilizes the mRNA (TFR1 or DMT1) and allows increased cellular iron uptake. Binding of IRPs to the 5′-UTR of ferritin or FPN mRNA decreases translation of these mRNAs, resulting in less storage and less export of iron in an iron-deficient cell. When intracellular iron concentrations increase, the fate of the 2 IRPs differs: IRP-1 is converted from an RNA-binding protein into an aconitase, whereas IRP-2 is degraded by a ubiquitin ligase complex. As a result, IREs are not occupied by IRPs, leading to decreased production of the iron uptake proteins TFR1 and DMT1 and increased translation of ferritin and ferroportin, protecting the cell from iron excess.

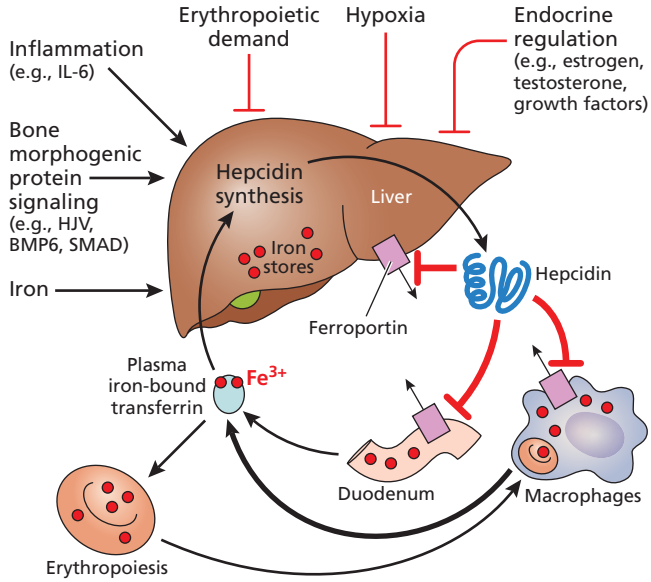
Within each cell, iron is destined for mitochondrial heme synthesis, iron-sulfur cluster synthesis, or incorporation into iron-containing enzymes or is stored within ferritin. Erythroid cells are by far the most avid consumers of iron and utilize it to synthesize heme, which complexes with globin proteins, forming hemoglobin. In erythroid cells, the first step in heme synthesis: The condensation of glycine and succinyl coenzyme A is catalyzed by δ-aminolevulinic acid synthase (ALAS) 2, an enzyme whose production is regulated by iron availability via the IRE-IRP system. ALAS2 mRNA contains a 5′-IRE, thus its translation is increased when cellular iron increases, providing a link between iron availability and heme synthesis. Erythrocytes survive in the circulation for approximately 120 d. Clearance of aged red blood cells occurs in the spleen and to some extent in the liver. In the spleen, senescent RBCs are hemolyzed and phagocytosed by macrophages of the red pulp. Hemoglobin is catabolized, and heme is subsequently degraded by the enzyme heme oxygenase to produce iron, biliverdin, and carbon monoxide. Iron is then either stored within ferritin in macrophages or released into the circulation via ferroportin.

The main form of cellular iron storage is ferritin, a 24-subunit nanocage that incorporates iron and renders it insoluble and redox inactive. Iron is recovered from ferritin through the process of ferritinophagy, mediated by the autophagy receptor NCOA4. Under conditions of high intracellular iron, NCOA4 is degraded through the action of HERC2 ubiquitin E3 ligase, and ferritin remains stable. When the cell is iron deficient, NCOA4 accumulates and triggers autophagy of ferritin, eventually resulting in the release of iron from lysosomes. Interestingly, the process of ferritinophagy is also utilized by erythroid precursors to deliver iron for hemoglobin synthesis. In contrast to intracellular ferritin, serum ferritin has a different composition of subunits, it is relatively iron poor, and its function is not understood.

Regulation of systemic iron physiology

Hepcidin is a 25–amino-acid peptide hormone produced mainly by the liver and is the major regulator of iron absorption and storage. Hepcidin regulates cellular iron egress by causing occlusion of ferroportin and its internalization and degradation. In this way, elevated levels of hepcidin inhibit iron absorption from the GI tract and prevent the release of iron from hepatocytes and macrophages (Figure 5-3). Hepcidin production is strongly regulated by iron (both circulating and stored), erythropoietic activity, and inflammation. Most of the mechanistic understanding of hepcidin regulation has been derived from animal models.

Figure 5-3 Regulators of iron balance. The hormone hepcidin regulates plasma iron concentration by controlling ferroportin levels on iron-exporting cells, including duodenal enterocytes, recycling macrophages of the spleen and liver, and hepatocytes. Hepcidin production is regulated by multiple stimuli: intracellular and extracellular iron concentration increase hepcidin transcription, as does inflammation, whereas erythropoietic activity suppresses hepcidin production. Reproduced from Steinbicker AU, Muckenthaler MU, *Nutrients*. 2013;5(8):3034-3061, with permission.



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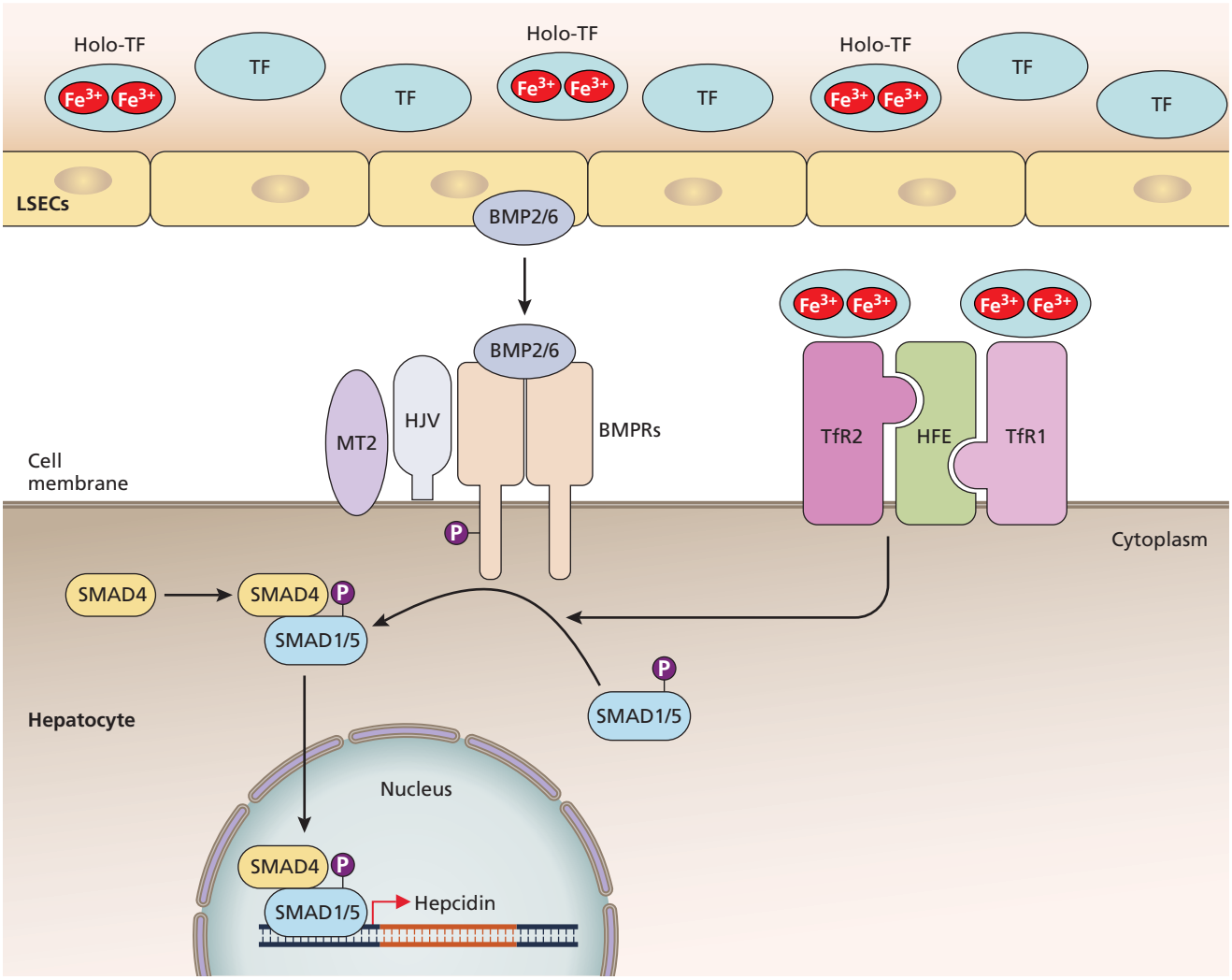
Hepcidin transcription is increased proportional to iron loading, which prevents further iron absorption and ensures the maintenance of body iron balance. Conversely, hepcidin levels are decreased in iron deficiency to allow greater iron absorption and correction of the body iron deficit. Iron-dependent hepcidin regulation is mediated by the bone morphogenetic protein (BMP) pathway (Figure 5-4). BMPs are members of the TGF-β superfamily and have pleiotropic roles in the body. BMP ligands bind to complexes of type I and type II serine and threonine kinase receptors, which phosphorylate receptor-activated sons of mothers against decapentaplegic proteins (SMADs) 1/5/8. These associate with SMAD 4, forming an activated SMAD transcription factor complex that increases hepcidin transcription. Another key hepcidin-regulatory molecule is hemojuvelin (HJV), which functions as a BMP coreceptor and facilitates interaction of specific BMP ligands and receptors. Mutations in HJV result in severe hepcidin deficiency and juvenile (type 2) hemochromatosis.

Several BMP ligands were reported to induce hepcidin expression in vitro, but mouse models have shown that BMP6 and BMP2 are important in vivo. Specifically, BMP6 and 2 are produced by the sinusoidal endothelial cells in the liver and act on hepatocytes to maintain

Figure 5-4 A model of the regulation of hepatic hepcidin expression. Regulated protein-protein interactions among HFE, TFR2, HJV (proteins mutated in HH), BMP receptors, and BMP ligands play a critical role in the regulation of hepcidin expression in hepatocytes in response to iron loading. BMP ligands that regulate hepcidin production are secreted by the liver sinusoidal endothelial cells (LSECs), and the rate of BMP6 production is regulated by liver iron stores. Holo-transferrin is "sensed" by TFR1/HFE complex and TFR2. Binding of holo-TF promotes interaction of HFE and TFR2 with the BMP receptor complex. Thus, higher holo-transferrin concentrations and higher iron stores lead to activation of BMP/SMAD signaling and hepcidin transcription. Modified from Silvestri L et al, *Vitam Horm*. 2019;110:71-99, with permission.



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baseline hepcidin expression. Furthermore, BMP6 production is induced by iron loading, mediating hepcidin induction in response to increased iron stores.

Extracellular iron-sensing (holotransferrin sensing) is dependent on TFR1, TFR2, and HFE, all expressed on hepatocytes. HFE is an MHC class I–like protein identified as a gene mutated in the most common form of hereditary hemochromatosis. HFE interacts with TFR1 but is displaced from the complex by holo-Tf (holotransferrin) binding to TFR1. Instead, HFE interacts with ALK3, a BMP receptor type I, and prevents its ubiquitination and degradation, thus stabilizing ALK3 protein on the surface of hepatocytes proportional to the concentration of holo-Tf. When holo-Tf concentrations are high, TFR2 protein is also stabilized by binding holo-Tf and likely interacts with HFE and HJV. Thus, it is thought that increasing holo-Tf concentration leads to the formation of a multiprotein complex centered on the BMP pathway and potentiates SMAD signaling (Figure 5-4). In hereditary hemochromatosis, defects in hepatocyte iron sensing lead to inappropriately low levels of hepcidin for the degree of iron present.

In iron deficiency, BMP signaling and hepcidin production are also downregulated by the hepatocyte cell surface serine protease transmembrane protease serine S6 (TMPRSS6). TMPRSS6 is stabilized during iron deficiency and binds to HJV and other components of the BMP pathway, inhibiting SMAD signaling and lowering hepcidin expression. Mutations in TMPRSS6 lead to inappropriately elevated hepcidin concentration and result in iron-refractory iron deficiency anemia.

Hepcidin is potently increased by inflammation, and this is mediated by interleukin (IL)-6 signaling (the JAK/STAT pathway), with synergistic contribution from the BMP pathway. Increased hepcidin causes hypoferremia, a host defense mechanism against extracellular pathogens, particularly gram-negative bacteria, whose rate of growth is strongly influenced by iron. However, when chronically elevated, hepcidin causes prolonged hypoferremia, leading to development of anemia of inflammation (anemia of chronic disease). Multiple hepcidin agonists and antagonists are under clinical development for the treatment of disorders of inappropriately low or high hepcidin levels, respectively.

Hepcidin production is suppressed by an increase in erythropoietic activity, for example, after hemorrhage or administration of erythropoietin (EPO). Erythropoietic hepcidin suppression is mediated by the recently described hormone erythroferrone (ERFE, see video file in online edition). ERFE is produced by erythroblasts in response to EPO during stress erythropoiesis. ERFE acts as a trap for BMP ligands, including BMP6 and 2, leading to decreased hepatic SMAD 1/5 phosphorylation and hepcidin expression. This allows iron absorption and release from storage to increase, providing greater iron availability for erythropoiesis.

Hereditary hemochromatosis and other iron overload disorders

Iron deposition in body tissues or organs is referred to as iron overload (hemosiderosis). Iron overload may lead to iron-induced injury in affected body tissues. Hereditary hemochromatosis is a congenital cause of iron overload resulting from increased gastrointestinal iron absorption. Other etiologies of iron overload are discussed in the following (Table 5-2).

Table 5-2 Causes of iron overload

Condition	Cause	Mechanism	Comments
1. Hereditary conditions			Increased iron absorption leads to elevated Tf saturation and appearance of NTBI; hepatocytes express the highest levels of NTBI transporters; therefore, hepatic iron overload usually predominates
i) Hereditary hemochromatosis		Impairment in the hepcidin/ferroportin axis	
HFE hemochromatosis	Point mutations in the *HFE* gene	Relative hepcidin deficiency	Amino acid substitutions; found primarily in Caucasians
TFR2 hemochromatosis	Mutations in *TFR2*	Relative hepcidin deficiency	Found in multiple ethnicities
HJV hemochromatosis	Mutations in HJV or compound heterozygote with HFE	Absolute hepcidin deficiency	Juvenile hemochromatosis
Hepcidin (HAMP) hemochromatosis	Mutation in HAMP	Absolute hepcidin deficiency	Juvenile hemochromatosis

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Table 5-2 *(continued)*

Condition	Cause	Mechanism	Comments
Ferroportin disease			
Classical	Heterozygous missense mutations in ferroportin	Unable to export iron	Loss of function, "macrophage type"
Nonclassical		Resistant to hepcidin	Gain of function, "hepatic type"
ii) Other congenital iron overload syndromes			
African iron overload	Possible polymorphism in ferroportin gene, compounded by high iron consumption	Increased transferrin saturation and ferritin	Hepatic and RES iron overload
Aceruloplasminemia	Mutations in ceruloplasmin gene	Decreased ferroxidase activity	Impairs ability to mobilize iron from macrophages and hepatocytes; neurological manifestations, DM, anemia
Atransferrinemia	Mutations in Tf gene	Unable to deliver iron to erythroid precursors	Increased GI iron absorption and deficiency of Tf leads to high NTBI and loading of parenchyma
iii) Congenital anemias (eg, β-thalassemia, hereditary sideroblastic anemia)		Ineffective erythropoiesis +/- transfusions	Increased GI absorption +/- RES overload Discussed in Chapter 7
2. Acquired clonal conditions (eg, myelodysplastic syndromes, myelofibrosis)		Transfusions +/- ineffective erythropoiesis	RES overload +/- increased GI absorption Discussed in Chapter 18
3. Iatrogenic	Inappropriate iron supplementation		Intravenous iron repletion for the anemia of renal failure; oral iron supplements for noniron deficiency causes of anemia

DM, diabetes mellitus; *HFE*, homeostatic iron regulator, the gene affected in hereditary HFE hemochromatosis; RES, reticuloendothelial system.

The toxicity of excess iron is mediated by its ability to catalyze generation of reactive oxygen species (ROS). Once the transferrin saturation is elevated (from 70% to 80%–85%, depending on the study), non–transferrin-bound iron (NTBI) appears in the circulation. A portion of NTBI is redox active and referred to as labile plasma iron, which promotes formation of ROS. NTBI is taken up by cells expressing NTBI transporters, leading to cellular iron overload. Excess intracellular iron damages subcellular components (Figure 5-5) and eventually causes organ dysfunction.

HFE hemochromatosis

Epidemiology and genetics

HFE hemochromatosis is the most common form of hereditary hemochromatosis. It is prevalent in individuals of Northern European descent because of the presence of the autosomal-recessive founder allele, C282Y. It is distinctly uncommon in other ethnicities. A G-to-A mutation at nucleotide 845 of HFE leads to a cysteine-to-tyrosine substitution at amino acid 282, the C282Y mutation. In some geographical areas (eg, the northern United Kingdom and Ireland), 10% to 15% of White persons are heterozygous for this mutation (C282Y/WT), though the clinical expression of iron damage in heterozygotes is rare. About 0.5% of the population in Northern Europe is homozygous for the C282Y/C282Y mutation, but homozygotes account for 60% to 90% of clinical cases of hereditary hemochromatosis. Significant variation exists in the phenotypic expression of HFE hemochromatosis. Although penetrance of biochemically defined iron overload (elevated transferrin saturation or ferritin level) is relatively high, penetrance of clinically defined iron overload is low and is affected by the presence of genetic modifiers and environmental and other risk factors, such as alcoholic hepatitis (Table 5-3).

A second mutation involves a G-to-C substitution at HFE nucleotide 187, leading to a histidine-to-aspartic-acid substitution at amino acid 63 (H63D). Up to 30% of Caucasians in some geographical areas are heterozygous for this allele. H63D is less penetrant than C282Y, and only a small minority of homozygotes (H63D/H63D) develop clinical features of iron overload. Heterozygotes for the H63D mutation (H63D/WT) do not develop biochemical or clinical evidence of iron overload. Compound heterozygotes (C282Y/H63D) occasionally may develop

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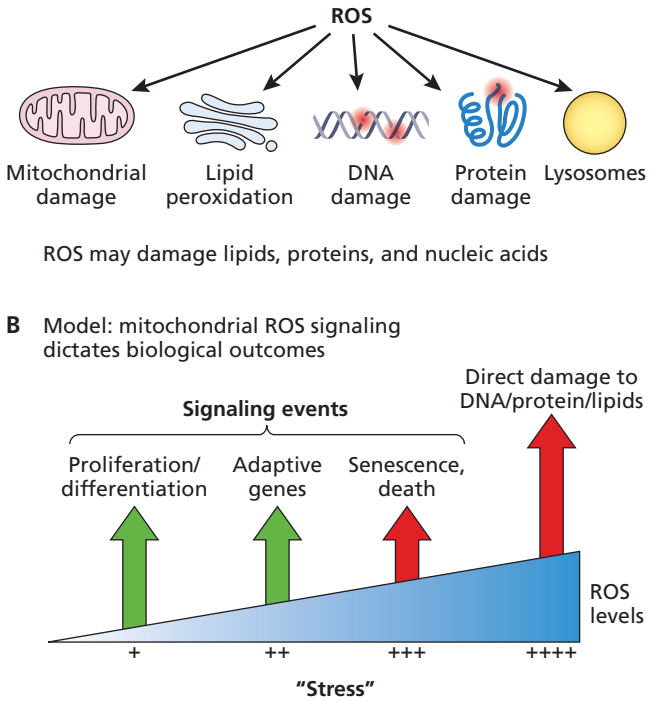

Figure 5-5 Cellular responses to oxidative stress. Once transferrin saturation is elevated (70% to 85%), NTBI appears in the circulation and is taken up by NTBI transporters on parenchymal cells. Excess iron in the circulation and intracellularly through Fenton chemistry causes the formation of ROS that damage cellular and subcellular components (A). Cellular consequences may include cell death or mutation and malignant progression (B). (A) Modified from Slotki I, Cabantchik ZI, *J Am Soc Nephrol*. 2015;26(11):2612-2619, with permission. (B) Redrawn from Hamanaka RB et al, *Trends Biochem Sci*. 2010;35:505-513, with permission.

mild iron overload and should be evaluated for coexisting risk factors if hemochromatosis is clinically expressed. In the United States, 15% to 30% of patients with clinical hemochromatosis have no identifiable HFE mutation.

Although homozygosity for the C282Y allele accounts for up to 90% of clinical hereditary hemochromatosis, the true phenotypic penetrance of HFE mutations remains a matter of debate. In a population screening study, 50% of C282Y homozygotes developed disease expression, typically by age 60. In a pedigree study of homozygous family members of known affected individuals, 85% of males and 65% of females had biochemical evidence of iron overload. Despite this, only 38% of males and 10% of females had disease-related symptoms, and 15% had fibrosis or cirrhosis on liver biopsy. Other studies suggested the clinical

Table 5-3 Prevalence of *HFE* genotypes among patients with hereditary hemochromatosis

Genotype	Prevalence among patients with hereditary hemochromatosis	Gene frequency in the population	Penetrance
C282Y/C282Y	60%-90%	0.5%★	13.5%†
C282Y/H63D	0%-10%		Low
C282Y/WT	Extremely rare	10-15%★	Low
H63D/H63D	0%-4%		Lower
H63D/WT	Extremely rare	20%‡	Not penetrant
WT/WT	15%-30%		Unknown
Private mutations	Rare		Unknown

Adapted from Cogswell ME et al, *Am J Prev Med*. 1999;2:134-140, with permission.
WT, wild type.
C282Y refers to a cysteine-to-tyrosine substitution at amino acid position 282. H63D refers to a histidine-to-aspartic-acid substitution at amino acid position 63.
★Caucasian population.
†European; clinical iron overload in all but C282Y homozygotes should prompt a search for contributing factors to iron overload.
‡Global population.

penetrance may be lower; symptoms were no more prevalent in homozygotes than in an unaffected control population, and the penetrance was estimated at less than 1%. The true clinical penetrance is uncertain but probably between 1% and 25%. Much of the variability in estimates is a result of different populations studied (blood donors versus preventive care clinics versus the general population versus family members of affected individuals) and how clinical penetrance was defined (iron studies versus liver function tests versus clinical symptoms versus liver biopsy).

Clinical presentation and diagnosis

The classic finding of a male with skin bronzing, hepatomegaly, and diabetes is an advanced (and now rare) presentation. Patients often present for evaluation of abnormal iron studies identified during routine physicals as part of screening when affected relatives are identified or when iron panels are drawn for other reasons. Despite a relatively common finding of abnormal biochemical iron tests, the clinical expression of iron-related organ damage is rare. Nevertheless, early diagnosis is important to prevent iron overload and avoid end-organ complications. The clinical presentation is varied and often nonspecific—such as fatigue, weakness, abdominal pain, arthralgias, and mild elevation of liver enzymes. Endocrine organs are commonly affected, and diabetes, hypothyroidism, and gonadal failure may occur. Both the mechanical and conduction systems of the heart may be affected, resulting in heart failure or arrhythmias. However, the earliest clinical sign of tissue damage is alterations in liver function tests, and

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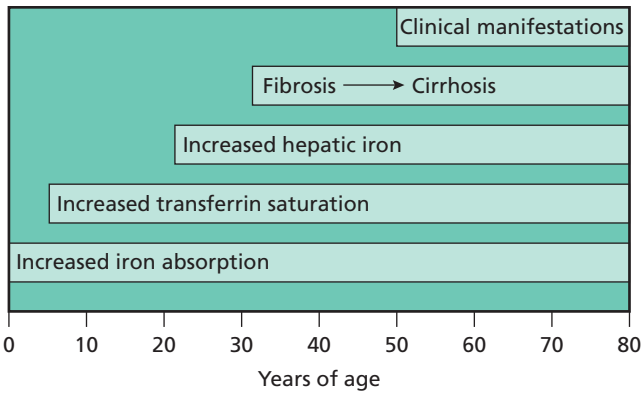

Figure 5-6 The natural history of hemochromatosis in relation to the liver in those individuals who develop clinical manifestations of iron overload. An increase in the percent saturation of transferrin can be detected in children homozygous for hemochromatosis. Increased liver iron stores generally can be detected in homozygous men by the end of the second decade. The serum ferritin concentration increases as hepatic iron stores increase. Hepatic fibrosis can be detected early in the fourth decade. Clinical manifestations generally occur in the fifth decade or later.

the earliest histologic sign is hepatic fibrosis. Iron-induced liver damage remains the most recognized complication of untreated disease (Figure 5-6).

The transferrin saturation in patients with hereditary hemochromatosis is higher than in normal individuals but shows considerable variability. A transferrin saturation >50% in males or >45% in females should prompt a fasting measurement and measurement of the serum ferritin level. Ferritin, though imperfect, is a reasonable surrogate for total body iron stores. Ferritin can be elevated in other conditions, including metabolic syndrome, inflammatory states, acute or chronic hepatitis, alcoholic liver disease, and others. In a population-based screening program performed through the Centers for Disease Control and Prevention, 11% to 22% of individuals with an elevated serum transferrin saturation had a concurrent elevation in serum ferritin level.

Molecular genotyping of the HFE locus, now a readily available test, should be considered if the diagnosis remains in question after secondary causes of iron overload have been ruled out or if affected family members exist.

Although liver biopsy was the historical gold standard for diagnosis of hepatic iron overload, noninvasive imaging tools are preferentially used to estimate body iron stores, including techniques including R2* or T2* magnetic resonance imaging (MRI) or superconducting quantum interference device (SQUID) susceptometry. MRI is available in an increasing number of centers and assesses iron deposition in the liver and heart and, more recently, the endocrine organs. SQUID is available in only a few centers worldwide. Newer techniques for measuring iron overload, such as dual energy computed tomography, have also been described. Imaging assessment of tissue iron loading is appropriate in individuals with elevated ferritin and TSAT in the absence of alternative explanations and in those with concern about organ injury (eg, elevated liver function tests, symptoms of heart failure). Liver biopsy could be considered when ferritin is ≥1000 μg/L, as the risk of (subclinical) advanced fibrosis/cirrhosis is high, and its detection is important for prognosis and surveillance of hepatocellular carcinoma.

A simple approximate method of estimating storage iron is by phlebotomy. If more than 4 g of iron (about 16 units of blood) can be mobilized without the patient becoming iron deficient, iron stores are at least 4 times normal.

Ultrasound-based elastography is increasingly used to assess for hepatic fibrosis. The principle is based on detecting altered liver stiffness (elasticity and viscosity) caused by fibrosis. Existing methods use mechanical excitation of the hepatic parenchyma to detect the tissue response, which differs between fibrotic and healthy tissue.

Liver biopsy can be performed on select patients to assess the extent of fibrosis and presence of cirrhosis or other causes contributing to liver injury (such as excess alcohol, nonalcoholic fatty liver disease or hepatitis C). Disadvantages of liver biopsy include the invasive nature, very limited sampling of the liver parenchyma, and potential for rare complications.

Treatment

Iron depletion prior to the occurrence of end-organ complications, such as cirrhosis, results in normal life expectancy. Phlebotomy of 1 unit of blood (400 to 500 cm^3 of whole blood; 200 to 250 mg of iron) should be initiated at 1- to 2-wk intervals and then tapered in frequency to maintain a ferritin level around 50 ng/mL, provided the hematocrit is maintained above 33% to 35%. Normal adults become iron deficient after 4 to 6 phlebotomies because the typical 1 g of iron stores is depleted. Patients with 4 g of storage iron do not become iron deficient until 16 to 20 phlebotomies have been performed. The clinical benefit of aggressive phlebotomy in moderate iron overload is less clear.

Phlebotomy is often effective at improving a patient's overall sense of well-being, resolving fatigue and malaise, normalizing skin pigmentation, and reducing elevated liver enzymes. Arthralgias, diabetes, and hypogonadism may not resolve, and cirrhosis or risk for hepatocellular carcinoma may not be reversed. It is important that patients understand that arthralgias in particular may not improve or may even worsen with phlebotomy.

Phlebotomy usually is not indicated and is only infrequently performed during adolescence. For hemochromatosis

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patients with advanced heart failure and hemodynamic instability, isovolemic erythrocytapheresis should be considered. If an isolated increase in fasting transferrin saturation is identified during screening, ferritin level should be monitored at 3- to 6-month intervals and phlebotomy initiated when the ferritin is >300 ng/mL in males or >200 ng/mL in nonpregnant females. Avoidance of alcohol and exogenous medicinal iron or iron-containing vitamins should be stressed. Dietary change aimed at avoiding iron-containing foods is often not necessary as long as patients are compliant with phlebotomy. Patients should be warned about the risks of eating raw seafood, undercooked pork, or unpasteurized milk because the incidence of severe *Vibrio vulnificus* and *Yersinia enterocolitica* infections increases in iron overload. The risk for mucormycosis may also increase if they begin chelation therapy. Iron chelation therapy should be considered if phlebotomy is contraindicated. Treatment of hepatic or other complications of iron overload is essential. Once cirrhosis develops, there is a >200-fold increased risk of hepatocellular carcinoma compared with the general population. Serial ultrasounds with or without measurement of α-fetoprotein may be employed to screen for hepatocellular carcinoma in at-risk individuals. Liver transplantation has been performed for end-stage liver disease in these patients.

Screening

Population screening for hereditary hemochromatosis is controversial and currently not recommended. However, early screening of at-risk individuals or families by measurement of fasting transferrin saturation, ferritin level, and HFE genotyping should be discussed. The possibility of genetic discrimination should be discussed before screening; for this reason, some authorities recommend against genetic screening before adulthood.

Other autosomal-recessive forms of hereditary hemochromatosis

Patients with HFE hemochromatosis rarely present before the fourth decade of life. Clinically significant iron overload in the 20s and 30s is more likely in the severe, early onset autosomal-recessive disorder juvenile hemochromatosis, which occurs because of recessive loss-of-function mutations in HJV or hepcidin. Juvenile hemochromatosis characteristically presents with life-threatening heart failure and polyendocrinopathies (eg, hypogonadotropic hypogonadism and impaired glucose tolerance or diabetes mellitus) more frequently than with liver dysfunction or other clinical manifestations. Patients often require intensive management of cardiac complications but may recover fully with an aggressive iron-depletion regimen. Recessive mutations in TFR2 are rare, and the disease phenotype is indistinguishable from HFE hemochromatosis other than a near-complete penetrance and possible presentation at an earlier age. Like HFE hemochromatosis, a common feature of these disorders is a relative deficiency of hepcidin for the degree of iron overload; the severity of the disease phenotype roughly correlates with the magnitude of hepcidin deficiency.

Neonatal hemochromatosis presents as perinatal liver failure and widespread systemic parenchymal iron deposition, but it is likely not a primary disorder of iron balance and appears to be a consequence of alloimmune hepatitis from a fetal-maternal antigen incompatibility. Treatment with intravenous immunoglobulin beginning in midgestation mitigates the severity of iron overload in newborns of mothers with a prior affected child.

Ferroportin disease

Iron overload resulting from autosomal dominant mutations in the gene *SLC40A1,* which encodes FPN1, is known as ferroportin disease. The most frequent form is from mutations that result in partial loss of FPN1 function ("classical ferroportin disease") due to an impairment in transport function or mistrafficking and decreased protein stability. In this condition, serum ferritin is often increased in the presence of a low-normal transferrin saturation or hemoglobin. These patients typically have substantial Kupffer cell iron storage early in their course. They often sustain an early decrease in serum iron and hemoglobin during phlebotomy, which may limit their tolerance of treatment.

Patients with a gain-of-function mutation ("nonclassical ferroportin disease") have clinical and histopathological features similar to autosomal-recessive forms of hemochromatosis. Characteristically, mutations affect the ability of hepcidin to bind or induce ubiquitination and degradation of FPN1, leading to a hepcidin-resistant phenotype. The patients display a spectrum of clinical phenotype, and though many require only careful monitoring, some may develop significant hepatic iron overload or other complications, such as arthropathy. It may be reasonable to assess tissue iron levels with imaging and institute treatment in affected individuals.

Other causes of iron overload

Many chronic anemias, particularly the thalassemias, are associated with clinically significant iron overload (Table 5-2). Iron overload in these patients can be due to transfusion, increased iron absorption, or both. Ineffective erythropoiesis, the intramedullary death of developing red blood cells, leads to inappropriately increased iron absorption through suppression of hepcidin production, likely via erythroferrone (see video file in online edition). Ineffective erythropoiesis can lead to significant

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iron-related morbidity even in the absence of transfusion in patients with thalassemia intermedia and other non–transfusion-dependent anemias. Blood transfusions are the predominant cause of iron overload in patients with thalassemia major, aplastic anemia, pure red cell aplasia, myelodysplastic syndromes (MDSs), and sickle cell anemia.

Less severe forms of iron overload have been described with alcoholic cirrhosis, hepatitis C virus infection, nonalcoholic steatohepatitis, and porphyria cutanea tarda (PCT). In some of these disorders, the frequency of HFE mutations is higher than would be predicted by chance and likely contributes to the risk of iron overload. Hereditary aceruloplasminemia may mimic hemochromatosis but is characterized by normal transferrin saturation and the presence of neurologic deficits, such as ataxia and dementia. Symptoms appear in adulthood, making an early diagnosis difficult. This disorder is extremely rare, and the exact incidence is unknown, but it may be more prevalent in Japan. As ceruloplasmin has ferroxidase activity that is important for the release of iron from macrophages, patients with a mutated gene may accumulate excess iron. Finally, aggressive intravenous iron administration in conditions such as the anemia of renal failure has been reported to result in iron overload.

Iron chelation therapy

The management of secondary iron overload may be challenging. Anemia often exists, requiring red blood cell transfusions and making phlebotomy impractical. In some cases, erythropoiesis-stimulating agents, such as erythropoietin, can be used to increase the hematocrit to a range safe for phlebotomy. Splenectomy may decrease transfusion requirements in some anemias. Treatment of the underlying condition, as in aplastic anemia, MDS, or myelofibrosis, should be undertaken if possible.

In situations in which the removal of excess iron is desirable but phlebotomy cannot be used, iron chelation therapy may be considered. There is considerable experience with this treatment in the hemoglobinopathies, wherein decreasing organ and total body iron has been demonstrated to prevent and even reverse organ dysfunction. All three available chelators (subcutaneous deferoxamine and the oral agents deferiprone and deferasirox) are able to reduce total body, hepatic, and myocardial iron overload, and no single drug or combination of drugs is currently considered the preferred therapy. There is increasing experience with iron chelation therapy in acquired anemias, conditions in which at least some patients appear to benefit from reduction of iron overload. There is a body of preclinical evidence suggesting that some benefit of iron chelation therapy in these conditions may be from removal of labile iron and its toxic effects; labile iron is suppressed very rapidly with chelation within minutes to hours (Figure 5-5), as opposed to removal of total body iron, which takes months to years.

All chelators have potential side effects and require appropriate monitoring, as per the product monographs and as summarized in Tables 5-4 and 5-5. The first available iron chelation agent was deferoxamine, which has

Table 5-4 Iron chelation agents currently available for clinical use; properties and indications

Property	Deferoxamine	Deferiprone	Deferasirox
Usual dose	20-60 mg/kg/d	75-100 mg/kg/d	20-40 mg/kg/d
Route	Subcutaneous, intravenous	Oral	Oral
	>8-12 h, >5 d/wk	3 times daily	Once daily
Half-life	20-30 min	3-4 h	8-16 h
Excretion	Urinary, fecal	Urinary	Fecal
Side effects★	Injection-site reaction	Agranulocytosis (rare)	Renal insufficiency in up to 1/3‡
	Potential ocular and otic toxicity†		GI disturbance
Indications	Chronic IOL from transfusion-dependent anemias	IOL from RBC transfusions in adult and pediatric patients 3 y of age and older with thalassemia syndromes, sickle cell disease, or other anemias	IOL from RBC transfusion in patients ≥2 y old (United States) or ≥6 y old (Europe)
	Acute iron intoxication		IOL when DFO contraindicated or inadequate in: Other anemias Age 2-5 y (Europe)

Updated from Leitch HA, Vickars LM, *Hematology Am Soc Hematol Educ Program*. 2009;2009:664-672, with permission from the American Society of Hematology.

DFO, deferoxamine; IOL, iron overload; RBC, red blood cell.

★Monitoring as per product monograph for all agents.

†Yearly monitoring recommended for all.

‡Usually reversible or nonprogressive.

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Table 5-5 Assessment of iron overload and common adverse events of chelators

Observation	Frequency	IOL assessment	AE monitoring
Iron intake rate	Each transfusion	√	
Chelation dose and frequency	Every 3 mo	√	√
Renal function*	As frequently as required		√
Liver function	Every 3 mo	√	√
Sequential serum ferritin, transferrin saturation†	Every 3 mo	√	
GTT, thyroid, calcium metabolism (BMD‡)	Yearly in adults	√	
Liver iron (T2* MRI)§	At baseline when feasible and subsequently as clinically indicated	√	
Cardiac function (echo, MRI, ECG)	At baseline, then as clinically indicated	√	
Cardiac iron (T2* MRI)	For patients receiving >50 U RBCs prior to ICT or with CHF or arrhythmias	√	
Slit lamp examination, audiometry	Yearly		√

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Ideal assessments are listed, and mandatory assessments are shown in boldface type.

AE, adverse event; BMD, bone mineral density; CHF, congestive heart failure; ECG, electrocardiogram; echo, echocardiogram; GTT, glucose tolerance test; ICT, iron chelation therapy; IOL, iron overload; RBC, red blood cell; U, unit.

*Creatinine should be measured at least every 2 wk with each dose increase until stable.

†Transferrin saturation >80% may indicate the presence of oxidative stress (Sahlstedt L et al, *Br J Haematol*. 2001;113:836-838).

‡Based on early/suggestive data in transfusion dependent hemoglobinopathies (Ezzat H et al, *Blood*. 2012;120(21):abstract 3203).

§Up to 25% of hepatic IOL is underestimated by serum ferritin level (Gattermann N et al, EHA Annual Meeting 2013, poster 419).

been used extensively in hemoglobinopathy patients, and good compliance with chelation in patients with β-thalassemia major improved their median survival from the teens to near normal. Deferoxamine is administered by daily continuous subcutaneous infusion (up to 40 mg/kg) over an 8- to 12-hour period. Local injection site complications are frequent and can be minimized by rotation of injection sites, addition of hydrocortisone to the infusion, antihistamines, or local measures. The potential ocular and auditory complications of deferoxamine mandate annual audiologic and ophthalmologic evaluations. Chronic deferoxamine therapy may be arduous, and suboptimal compliance often limits potential benefits.

Deferasirox was the first oral iron chelator to receive approval from the US Food and Drug Administration. In a prospective trial, 20 to 30 mg/kg of deferasirox daily (dispersible formulation; DF) reduced LIC, serum ferritin levels, and transaminases that were elevated at baseline prechelation. Adverse events related to the GI tract are frequent with deferasirox and may require dose reductions or other measures (published guidelines are available). Approximately one-third of patients experience an increase in serum creatinine, which is usually reversible. Ocular and auditory disturbances are more frequent with deferoxamine at a ferritin level <1000 ng/mL, and with deferasirox, this does not seem to be the case. The film-coated tablet formulation of deferasirox (FCT) has recently become available. The FCT has fewer GI side effects than the DF and is generally reported by patients as being more convenient. Because of differences in bioavailability, dosing of the FCT in milligram per killigram is 30% less than with the DF.

In the United States, the most recently approved oral iron chelator is deferiprone, which is dosed 3 times daily. Side effects include GI upset, arthralgias, and elevated hepatic enzymes. Drug-induced neutropenia or agranulocytosis requires weekly monitoring of blood counts. Though typically not used for acquired anemias because of the potential for agranulocytosis, some small studies in this setting demonstrate safety and efficacy. Deferiprone appears to be particularly effective in reducing cardiac iron overload, which may be a function of its ability to cross the cell membrane. Experience with deferasirox (which also crosses cell membranes) for this indication is accumulating.

In some circumstances, intensification of chelation may be desirable. For example, it has been shown in β-thalassemia major that a ferritin level over 2500 ng/mL portends inferior cardiac disease-free survival. Continuous infusions of deferoxamine or combination regimens

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should be considered in this circumstance at least until cardiac iron status and left ventricular ejection fraction are documented as negative and normal, respectively, and preferably until the ferritin level is consistently <2500 ng/mL. For patients with documented cardiac iron loading or decreased left ventricular ejection fraction, intensive chelation may partially or fully reverse these complications, and combination therapy with deferoxamine and deferiprone, or 24-hour infusions of deferoxamine, should be strongly considered. Combinations of deferoxamine and deferasirox were investigated in small studies with good results. Combinations of deferiprone and deferasirox have not been extensively studied. Deferasirox as a single agent does improve cardiac iron-related abnormalities; however, intensification of the dose appropriate to the clinical situation may or may not be limited by side effects requiring dose interruptions and adjustments, and it is important to address iron-related cardiac complications in a timely manner. Until the treating physician has accumulated experience and a comfort level with the use of these agents, the expected side effects, and the monitoring required, input from a hematologist with appropriate expertise should be considered.

Treatment of the acquired anemias is discussed in detail in Chapter 18, but a few words on chelation in these disorders may be appropriate here. Transfusions and iron chelation therapy are generally considered to be supportive care for acquired anemias. For MDS, the goal of active therapies, such as erythropoiesis-stimulating agents, immunomodulatory agents, or immunosuppressive therapies for lower-risk disease and hypomethylating agents for higher-risk disease, is hematologic improvement, including an erythroid response and transfusion independence. The achievement of transfusion independence is widely recognized to improve survival and quality of life in these patients. The first prospective, placebo-controlled trial, TELESTO, showed moderate benefit of iron chelation in reducing morbidities associated with iron overload in transfusion-dependent, lower-risk MDS. Deferasirox or placebo was administered for at least 1 year, with the chelated group having modestly longer event-free survival and a trend toward longer overall survival. However, the study closed prematurely because of lagging patient enrollment. Additional nonrandomized studies of iron chelation therapy in MDS and fewer in the less common conditions aplastic anemia and myelofibrosis suggested superior survival in patients receiving chelation compared with patients not receiving chelation, and in multiple (but not all) studies of MDS, an erythroid response rate around 20% was seen with chelation, including the achievement of transfusion independence. Similar responses have been reported in myelofibrosis and may occur with more frequency in aplastic anemia. Patient characteristics predictive of erythroid response are currently unclear.

Guidelines for chelation in MDS are extrapolated from experience with deferoxamine in hemoglobinopathies and, for example, suggest chelation once the ferritin level is >1000 ng/mL or the transfusion burden >20 units of packed red blood cells. In the future, it may be more appropriate to institute (nondeferoxamine) chelation at lower doses to prevent iron overload rather than trying to rescue damaged tissue and being unable to increase the dose appropriately for the degree of iron overload because of side effects. This approach, however, should be confirmed to be safe and effective in clinical trials before it can be considered for routine practice. Among the new treatment strategies, luspatercept, which traps select TGF-β superfamily ligands, may help reach transfusion independence in either non–transfusion-dependent thalassemia or MDS.

KEY POINTS

- The absorption of iron by enterocytes and release of recycled iron from macrophages are tightly regulated by the interaction of the hormone hepcidin and iron transporter ferroportin.
- Iron overload may be due to hereditary or acquired causes or due to repeated blood transfusions.
- The HFE C282Y/C282Y is the most common genotype leading to clinical iron overload in hereditary hemochromatosis, but the clinical penetrance of the HFE C282Y/C282Y genotype is relatively low.
- Some clinical manifestations of hemochromatosis are reversible, but cirrhosis and the risk for hepatocellular carcinoma in cirrhotic patients are not.
- Population screening is controversial, but high-risk individuals (fasting transferrin saturation >45%, first-degree relative affected, Caucasian heritage) should be screened.
- Clinical manifestations of iron overload are similar regardless of etiology.
- Phlebotomy to remove excess iron is the primary treatment for conditions of iron overload not limited by anemia.
- Iron chelation therapy with deferoxamine, deferasirox, or deferiprone is an option when phlebotomy is not possible. Monitoring, including regular creatinine levels and other chemistry, and annual audiologic and ophthalmologic examinations are required in individuals treated with these agents, and monitoring for agranulocytosis is mandatory in case of deferiprone.

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The porphyrias

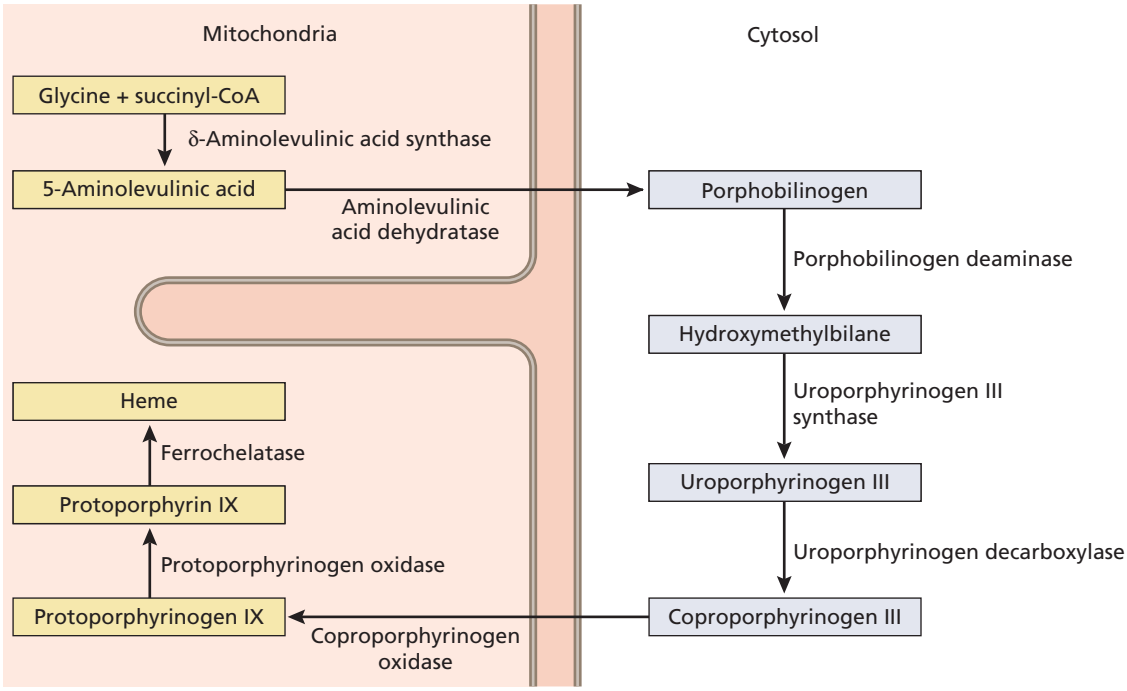
Introduction

Porphyrias are a group of disorders that result from enzymatic defects in the heme biosynthetic pathway leading to accumulation of porphyrins and their precursors in the body. The word "porphyria" is derived from the Greek word *porphuros*, meaning reddish-purple because in some porphyrias, purple-red porphyrins build up in the urine and exhibit red fluorescence on exposure to ultraviolet light. Porphyrins are tetrapyrroles, one of which (protoporphyrin IX) complexes with iron to form heme, a cofactor crucial for multiple biologic reactions and functions. Heme synthesis occurs in virtually all cells, but majority of heme is made in the bone marrow (about 85%), as it is required for hemoglobin and liver (about 15%), where it is required in the formation of several enzymes, most notably hepatic cytochrome P450 enzymes (CYPs).

Heme synthesis

The first step in heme synthesis is condensation of glycine and succinyl CoA to form δ-aminolevulinic acid (ALA) in the mitochondria, catalyzed by the enzyme ALAS (Figure 5-7). Six additional enzymes are involved in the reactions that convert ALA to protoporphyrin, with some reactions occurring in the cytoplasm and others in the mitochondria. Specifically, ALA dehydratase (ALAD; in the cytoplasm) results in formation of porphobilinogen (PBG); PBG deaminase (PBGD; cytoplasm) results in formation of hydroxymethylbilane; uroporphyrinogen III synthase (UROS; cytoplasm) results in formation of uroporphyrinogen III; uroporphyrinogen decarboxylase (UROD; cytoplasm) results in formation of coproporphyrinogen III; coproporphyrinogen oxidase (CPO; mitochondria) results in formation of protoporphyrinogen; and protoporphyrinogen oxidase (PPO; mitochondria) results in formation of protoporphyrin IX. The final step in heme synthesis is the coupling of protoporphyrin IX to iron in the mitochondria, catalyzed by ferrochelatase (FECH). Although the steps are similar in erythroid cells and hepatocytes, control of heme production differs between these tissues, mainly due to differences in the regulation of ALA synthesis, which is coded by 2 different genes, *ALAS1* and *ALAS2*. In the liver, ALAS1 is the rate-limiting enzyme, and its production is regulated by heme through negative feedback: it is downregulated by increased heme levels and upregulated by decreased heme. Since most heme synthesized in the liver goes toward the production of hepatic

Figure 5-7 The heme biosynthetic pathway. Glycine and succinyl CoA are condensed to δ-ALA in the mitochondria, catalyzed by ALAS. Six additional enzymes localized in the cytoplasm or mitochondria convert ALA to protoporphyrin. Protoporphyrin is coupled to iron to form heme. The rate of ALA synthesis is controlled in the liver by ALAS1, which is downregulated by increased heme and glucose levels and induced by certain steroids, drugs, chemicals, and stress. In erythroid cells, the rate of ALA synthesis is regulated by iron availability.



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CYPs, their induction leads to the utilization of heme and induction of ALAS1. The *ALAS1* gene and certain cytochrome genes share upstream enhancer elements, which coordinate induction of these genes.

ALAS2 is constitutively expressed in erythroid cells, and, in contrast to ALAS1, it is not negatively regulated by heme. Rather, ALAS2 production is increased during erythroid differentiation via erythroid-specific transcription factors like GATA1. Furthermore, ALAS2 is posttranscriptionally regulated by iron due to the presence of a 5′-IRE in ALAS2 mRNA (but not ALAS1 mRNA). Increased iron availability leads to decreased IRP binding to 5′-IRE and allows translation of ALAS2 to proceed. Other enzymes in the heme synthetic pathway are also upregulated in the bone marrow during erythroid maturation to enhance hemoglobin synthesis. One practical implication of this difference is that heme can be used to treat an exacerbation of acute hepatic porphyrias (AHPs), such as acute intermittent porphyria (AIP), downregulating ALAS1 activity. Conversely, certain steroids, chemicals, and stress can trigger exacerbations of hepatic porphyrias by inducing ALAS1. Glucose suppresses ALAS1 expression, and this explains the higher incidence of exacerbations while fasting and remissions observed in response to glucose infusions.

Pathophysiology

The different porphyrias arise from a deficiency of different enzymes in the heme biosynthetic pathway (see Table 5-6), resulting in accumulation of porphyrins and their precursors in a pattern specific to the enzyme involved, which is also reflected in the respective clinical manifestations (see video file in online edition). Enzyme deficiency primarily results from mutations affecting the gene that encodes the relevant enzyme, but rarely, the mutations can also affect a regulatory gene rather than the enzyme itself. During an acute exacerbation of the AHPs, the porphyrin precursors ALA and PBG are released in large amounts by the liver and are potentially neurotoxic. Characteristic skin symptoms develop from interaction of light with porphyrins that are transported to the skin. This occurs because porphyrins absorb light and emit energy, which results in cell damage by peroxidation of lipid membranes, thus disrupting intracellular organelles and other mechanisms. A principal site of photosensitivity in some porphyrias is blood vessels of the papillary dermis. Conventionally, symptomatic episodes in patients with AHPs have been referred to as acute attacks. As patients can go without symptoms for long periods of time and yet the underlying condition remains, we have referred to symptomatic episodes as exacerbations.

Inheritance

Most of the porphyrias are inherited in an autosomal dominant fashion with incomplete penetrance, whereas some types are autosomal recessive, X-linked, or compound heterozygous. The penetrance of porphyrias varies, with only about half of gene carriers demonstrating clinical manifestations. Porphyria cutanea tarda is primarily due to an acquired inhibition of UROD with a heterozygous UROD mutation contributing to about 20% of cases.

Classification

Porphyrias can be classified as hepatic or erythropoietic porphyria based on the organ in which accumulation

Table 5-6 Classification of porphyrias

Type of porphyria	Inheritance pattern	Enzyme affected	Organs involved	Symptoms	Treatment	Comments
Acute porphyrias						
AIP	AD	Porphobilinogen deaminase/hydroxymethylbilane synthase	NS, liver	NV	Glucose Hemin Supportive care* Liver transplant Gene therapy siRNA	No cutaneous symptoms Port wine–colored urine Common in Sweden
VP	AD	Protoporphyrinogen oxidase	NS, skin, liver	NV, cutaneous	Glucose Hemin Supportive care* Liver transplant Gene therapy	Common in South Africa
HCP	AD	Coproporphyrinogen oxidase	NS, skin, liver	NV, cutaneous	Glucose Hemin Supportive care*	Skin lesions occur but not common

Table continues on next page

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Table 5-6 Classification of porphyrias *(continued)*

Type of porphyria	Inheritance pattern	Enzyme affected	Organs involved	Symptoms	Treatment	Comments
ADP	AR	ALA dehydratase	NS, liver	NV	Glucose Hemin Supportive care*	Very rare, chronic neuropathy ALA alone increased Late-onset type associated with MPN
Blistering cutaneous porphyrias						
PCT	AD	Uroporphyrinogen decarboxylase	Skin, liver	Cutaneous	Control liver IOL Protect from sun/light exposure	Sporadic (80%) and familial forms exist
CEP	AR	Uroporphyrinogen III synthase	Skin, RBC	Cutaneous, hemolytic anemia	Suppress erythropoiesis HSCT	Erythrodontia (teeth fluoresce) Red fluorescent urine Bone changes Rare cases of CEP: caused by mutations in *GATA-1*, transcription factor regulating UROS expression
Hepatoerythropoietic porphyria (HEP)	AR	Uroporphyrinogen decarboxylase	Skin, RBC, liver	Cutaneous, hemolytic anemia	Sun/light protection	Lab results similar to PCT Red urine
Nonblistering cutaneous porphyrias						
EPP	AR	Ferrochelatase	Skin, RBC, liver	Cutaneous (nonblistering)	Sun/light protection Beta carotene Afamelanotide Measures for gallstones Liver + HSCT	Burning sensation in photosensitive areas Microcytic anemia Late-onset type associated with MDS Rare autosomal dominant EPP: mutations in *CLPX*, a regulator of ALAS2
XLP	X-linked	ALAS2 gain of function	RBC, skin, liver	Cutaneous nonblistering	Sun/light protection Beta carotene Afamelanotide Measures for gallstones Liver + HSCT	Phenotypically similar to EPP Elevated erythrocyte zinc protoporphyrin compared with EPP FECH function is intact

In all conditions that involve the liver, chronic liver failure and hepatocellular carcinoma may develop.

*See Table 5-7 for supportive care measures.

AD, autosomal dominant; AR, autosomal recessive; HSCT, hematopoietic stem cell transplantation; IOL, iron overload; MPN, myeloproliferative neoplasm; NS, nervous system; NV, neurovisceral; RBC, red blood cell.

of porphyrins and their precursors primarily occurs—liver or bone marrow respectively. Additionally, they are classified as acute (with neurological manifestations) or cutaneous (with either blistering or nonblistering photosensitivity), with some overlap between these categories (Table 5-6).

Acute porphyrias

Four porphyrias present with acute features, including the most common—AIP, hereditary coproporphyria (HCP), variegate porphyria (VP)—and the ultrarare δ-ALA dehydratase porphyria (ADP). These are also known as the AHPs.

Acute intermittent porphyria

AIP, also known as Swedish porphyria, results from deficient activity of PBGD. PBGD is also known as hydroxymethylbilane synthase (HMBS). It affects about 1 in 75,000 people of European descent, except in northern Sweden, where 1 in 1000 are affected. AIP does not have skin manifestations unless the disease is complicated by chronic kidney disease. Heterozygous mutations underlying AIP typically reduce the activity of PBGD by around 50%. This does not result in symptoms unless there is induction of the rate-limiting hepatic enzyme ALAS1, which can occur because of some medications,

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endocrine factors, and reduced calorie intake. High levels of PBG contribute to the reddish or port wine–colored urine seen in AIP. Erythrocyte PBGD activity is decreased in most patients, but about 5% have de novo mutations only in hepatocytes, in which case detection of the PBGD mutation confirms the diagnosis. There are 2 isoenzymes of PBGD: a ubiquitous form and an erythroid-specific enzyme. There are more than 300 mutations that are identified in AIP, and nearly all of them affect the ubiquitous hepatic PBGD but not the erythroid form.

Other acute porphyrias

VP, which occurs as a result of deficiency of protoporphyrinogen oxidase and HCP due to a deficiency of coproporphyrinogen oxidase, presents with either cutaneous photosensitivity or neurovisceral symptoms. Cutaneous manifestations are from an accumulation of photosensitizing porphyrins. Skin lesions may develop in about 60% of patients with VP and 5% with HCP, usually many days after sun exposure and typically on the back of the hands with fragility, blistering, and scarring. VP is most common in South Africa due to a founder effect, wherein a mutation, Arg59Tryp, occurs in families of Dutch descent. VP and HCP, like AIP, have autosomal dominant inheritance. Recessive cases of AIP, VP, and HCP have also been described in children with neurological and cutaneous symptoms with developmental delay. ADP, also known as doss or plumboporphyria, is the only acute porphyria that has autosomal-recessive inheritance. In contrast to the other acute porphyrias, ALA is increased in the urine and not PBG. Urine coproporphyrin III and erythrocyte zinc protoporphyrin are also markedly increased.

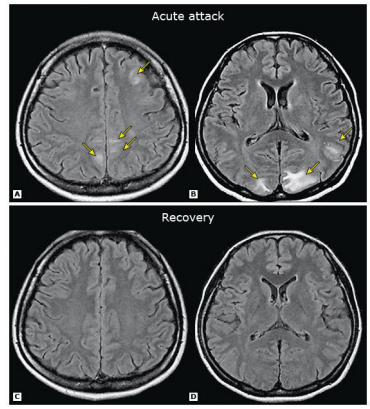
Clinical features of acute porphyria

The predominant manifestations of acute porphyrias are neurovisceral. Exacerbations can begin with restlessness and insomnia and may progress rapidly. The classic triad of symptoms seen in acute porphyrias include abdominal pain, peripheral neuropathy, and a variety of central nervous system manifestations.

Visceral symptoms typically include abdominal pain (the most common symptom), vomiting, constipation, and bladder paresis. Pain in the back or extremities is common. Features that help differentiate acute porphyrias from an acute abdomen include poor localization, absence of peritoneal signs or fever, and absence of leukocytosis. The pathogenesis of pain and other neuropathic manifestations is not well understood, but the elevated delta-ALA (δ-ALA), which is also elevated in lead poisoning and hereditary tyrosinemia, has been suggested to be neurotoxic and potentially responsible for causing pain. The most common clinical signs are tachycardia and hypertension suggestive of autonomic dysfunction and elevated levels of catecholamines, which can lead to arrhythmias and even cardiac arrest.

Peripheral neuropathy occurs in about 40% (especially with prolonged exacerbations) of acute porphyria exacerbations usually following the onset of abdominal symptoms. Motor neuropathy is predominant and laboratory testing can readily differentiate AHPs from disorders like Guillain-Barré syndrome. Proximal muscles are predominantly affected, with upper-limb involvement in about 50% cases. Sensory neuropathy, when it occurs, may have a bathing-trunk distribution, whereas cranial nerve involvement generally develops later. Respiratory muscle weakness and respiratory failure may develop, whereas central nervous system involvement may be manifested by agitation, disorientation, and seizures. Hyponatremia may result from the syndrome of inappropriate ADH-secretion or gastrointestinal losses. The cerebrospinal fluid (CSF) analysis in porphyria patients is expected to be normal. Imaging may demonstrate changes consistent with posterior reversible encephalopathy syndrome (PRES) (Figure 5-8). The mechanism of neuronal damage in acute porphyrias is not well understood. Vasospasm resulting from decreased nitrous oxide production by nitrous oxide synthase, a hemoprotein, or neurotoxicity from porphyrin precursors taken up into neurons has been suggested. The fact that neurologic manifestations occur because of heme production

Figure 5-8 Brain MRI images showing posterior reversible encephalopathy syndrome in AIP, in which central nervous system involvement may develop. The mechanism of neural damage in AIP is not well understood but might involve potentially neurotoxic effects of porphyrin precursors. Adapted from Kuo HC et al, *Eur Neurol.* 2011;66(5):247-252, with permission. Copyright © 2011 Karger Publishers, Basel, Switzerland.



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by the liver is supported by dramatic responses to liver transplantation. Many porphyria patients are described as having a psychiatric disorder. Psychiatric disturbances, including depression, hallucinations, and frank psychosis, are seen in acute porphyria. Nonspecific symptoms, such as fatigue, are also common in as many as 50% of cases.

Acute porphyrias commonly are associated with abnormalities in liver function tests suggesting chronic liver disease and have a significantly higher risk of hepatocellular carcinoma. Because serum α-fetoprotein may not always be raised, regular screening for HCC using imaging is advisable in adult patients. Chronic renal impairment may develop as a complication of AHP because of hypertension, although repeated vasospasms during recurrent attacks have also been implicated.

Triggers of acute porphyrias

Many medications can precipitate exacerbations of acute porphyria by inducing hepatic CYPs and ALAS-1. Safe and unsafe medications are listed at http://www.porphyria-europe.com and http://www.drugs-porphyria.org. Although some medications are absolutely contraindicated, others are only potentially dangerous, and the risk versus benefit of these medications should be considered on a case-by-case basis.

Acute episodes are more common in women during the second to fourth decades, occurring rarely before puberty and after menopause. Menstrual cycles are a common precipitant, with recurrent episodes described typically in the late luteal phase, as progesterone is implicated in increased heme catabolism. Oral contraceptives may aggravate exacerbations, whereas postmenopausal hormone replacement therapy does not seem to be a trigger. Other common aggravating factors are fasting, infections, certain medications, and alcohol intake. Alcohol induces or inhibits enzymes in the heme biosynthetic pathway (eg, ALAS1) and hepatic CYPs.

Diagnosis of acute porphyria

An index of suspicion for acute porphyria must be maintained, as delayed treatment may result in serious consequences, such as neurologic damage and even death. Consider acute porphyria in patients presenting with abdominal pain of unclear etiology and when other common etiologies have been excluded. Because of delays in diagnosis, porphyria patients may undergo multiple abdominal surgeries and other treatments without benefit.

Urine PBG level is the most important screening test for diagnosis of acute porphyria. Urine total porphyrins should also be measured simultaneously because these may remain elevated longer than PBG especially in the VP and HCP subtypes. If urine PBG and porphyrins are normal at or near the time of symptoms, it effectively excludes the diagnosis of 3 of the 4 acute porphyrias—AIP, VP, and HCP. The fourth and rarest acute porphyria, ADP, has elevated urine ALA and porphyrin levels but a normal urine PBG. Initial rapid testing for urinary PBG, ALA, and total porphyrins levels at the time of symptoms is recommended as a screening test. Rapid testing may be difficult due to limited availability of these tests. If these screening tests are positive, extended testing should be pursued for confirmation and to determine the acute porphyria subtype. Measurement of ALA, PBG, and porphyrins with fractionation of individual porphyrins, plasma porphyrins with fluorescence scanning, and fecal porphyrin analyses can identify the specific type of acute porphyria. Plasma fluorescence scanning is a more specific test for VP than traditional fecal chromatography. Confirmatory test is identification of specific mutation associated with the genes, and this will also enable screening of family members. A proposed algorithm for diagnosis of acute porphyria is shown in Figure 5-9.

The clinical status of the patient is important in determining approach because, if critically ill, more rapid qualitative screening tests should be obtained. However, these tests may not be readily available, so empiric therapy might have to be started. Clinicians must understand the ordering system of the reference laboratory to ensure that appropriate tests are ordered and collected correctly to make a diagnosis. For example, some reference laboratories include testing for PBG or ALA in a random or 24-hour urine study, whereas with others these must be ordered separately. Measurements using random urine collection with results normalized to creatinine are preferred over 24-hour urines. If the urine sample is dilute, it may result in inaccurate results. Determinations using very dilute samples may lack accuracy.

A common clinical circumstance is an elevation of porphyrins and especially coproporphyrins in the urine of patients suspected of having a neuropathic porphyria. Nonspecific elevation of urinary porphyrins can be seen in many medical conditions other than porphyria. These patients usually have secondary coproporphyrinuria, with the critical diagnostic point being that they have normal PBG levels while symptomatic—a finding that excludes neuropathic porphyria if the urine was collected correctly at the time of symptoms. Another common outpatient circumstance is that all prior 24-hour urine tests were collected when asymptomatic. Since PBG levels can normalize between exacerbations, the patient should be instructed to collect a 24-hour urine sample during clinical symptoms. True exacerbations of acute neuropathic

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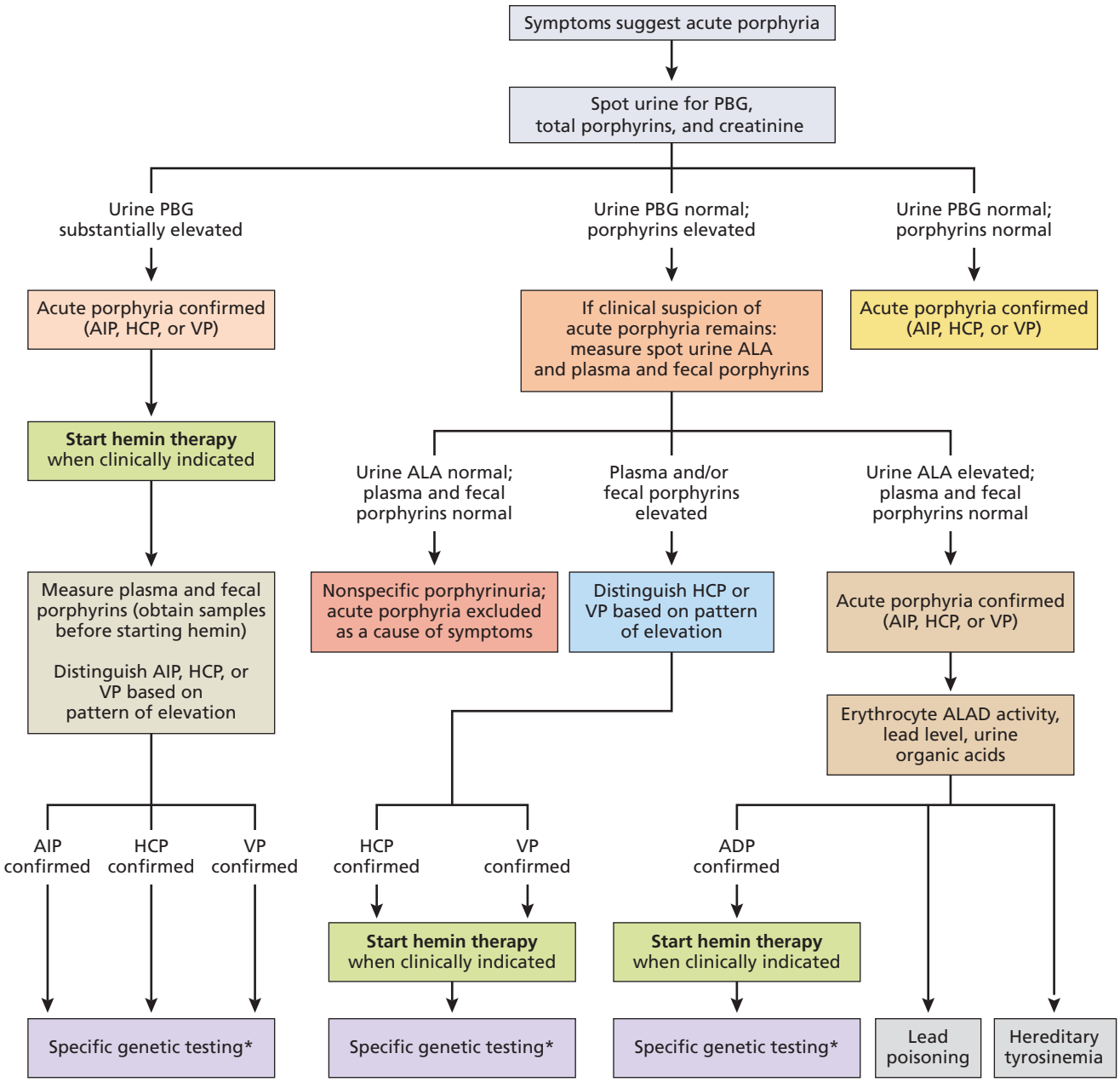
Symptoms suggest acute porphyria
Spot urine for PBG, total porphyrins, and creatinine
Urine PBG substantially elevated
Urine PBG normal; porphyrins elevated
Urine PBG normal; porphyrins normal
Acute porphyria confirmed (AIP, HCP, or VP)
If clinical suspicion of acute porphyria remains: measure spot urine ALA and plasma and fecal porphyrins
Acute porphyria confirmed (AIP, HCP, or VP)
Start hemin therapy when clinically indicated
Urine ALA normal; plasma and fecal porphyrins normal
Plasma and/or fecal porphyrins elevated
Urine ALA elevated; plasma and fecal porphyrins normal
Measure plasma and fecal porphyrins (obtain samples before starting hemin)
Distinguish AIP, HCP, or VP based on pattern of elevation
Nonspecific porphyrinuria; acute porphyria excluded as a cause of symptoms
Distinguish HCP or VP based on pattern of elevation
Acute porphyria confirmed (AIP, HCP, or VP)
Erythrocyte ALAD activity, lead level, urine organic acids
AIP confirmed
HCP confirmed
VP confirmed
HCP confirmed
VP confirmed
ADP confirmed
Start hemin therapy when clinically indicated
Start hemin therapy when clinically indicated
Specific genetic testing*
Specific genetic testing*
Specific genetic testing*
Lead poisoning
Hereditary tyrosinemia

Figure 5-9 Algorithm for diagnosis of acute porphyria and use of hemin in patients with symptoms suggesting an acute porphyria attack. Urine PBG may be tested by a screening method on-site (semiquantitative result, if available) or measured in a specialized laboratory (quantitative result, available in days to weeks). If available, a rapid method is extremely helpful because treatment can be initiated based on a positive result, and a negative result makes the diagnosis of an acute porphyria very unlikely. However, all symptomatic patients with suspected acute porphyria should have quantitative PBG, total porphyrins, and creatinine measured from the same sample. Because the results of quantitative testing are not known for days to weeks, we also order ALA and total porphyrins on the same urine sample. Urine creatinine is measured to allow normalization (results expressed per gram of creatinine). ADP, ALAD porphyria. *Performing genetic testing for the relevant porphyria following diagnosis may be used for further confirmation of the diagnosis and counseling of relatives and identification of other mutation carriers. Genetic testing is required to confirm a diagnosis of ADP. Reproduced from Anderson KE, Porphyrias: An overview. (UpToDate; 2021), with permission.

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porphyria are diagnosed easily and have abnormally high levels of PBG or ALA—usually in the order of 3 to 5 times the upper limit of normal.

The differential diagnosis of acute porphyria includes several disorders that are readily distinguished by laboratory testing; for example, in the case of lead toxicity, abdominal pain and neuropathy can coexist, and in paroxysmal nocturnal hemoglobinuria, abdominal pain and discolored urine occur in the absence of peripheral neuropathy (but in this case anemia occurs). The combination of peripheral neuropathy with central nervous system involvement is unusual in other conditions and should alert the clinician to the possibility of porphyria. Hereditary tyrosinemia type 1, which develops because of accumulation of succinyl acetone, an inhibitor of ALAD, can present in children with symptoms resembling acute porphyria.

Treatment of acute porphyria

Patients who present with acute porphyria usually require hospitalization for treatment and to monitor for complications. All contraindicated medications should be stopped. A multidisciplinary approach should be taken because the clinical manifestations encompass multiple organ systems. Severe episodes are characterized by abdominal pain requiring narcotics, vomiting, and inability to tolerate oral medications, neuropathy, and hyponatremia. Mild episodes may be treated initially with high carbohydrate intake of 2000 kcal/24 h orally or via a nasogastric tube. If this cannot be tolerated, intravenous 10% dextrose should be given targeting at least 300 g/d glucose, but precaution should be taken to avoid larger quantities, which may lead to hyponatremia. Even for mild attacks, hemin treatment is more effective and can prevent symptom progression and shorten hospitalizations. Opioids and phenothiazines or serotonin 5-HT3 receptor antagonists are often needed. Beta blockers can be used to treat tachycardia and hypertension.

Severe episodes require treatment with intravenous infusions of hemin (Figure 5-9), which binds to hemopexin and albumin in the plasma and is taken up by the liver hepatocytes, where it suppresses ALAS-1—the enzyme that catalyzes δ-ALA formation. The standard regimen is 3 to 4 mg/kg once daily of heme from lyophilized hematin reconstituted with human albumin in order to avoid thrombophlebitis (Panhematin; Recordati Rare Diseases Inc, Lebanon, NJ) or heme arginate (Orphan Europe Recordati) infused daily for 4 d or longer. Hemin should be started early for better clinical outcomes, and it is considered safe in pregnancy and renal impairment. Adverse effects include fever, hemolysis, and, without reconstitution with albumin, phlebitis. Response to therapy often begins within 1 to 2 d, particularly if commenced early.

Careful monitoring is advisable during acute attacks for early detection of complications (Table 5-7). At hospital discharge, advice should be provided for measures to prevent future exacerbations (Table 5-8). Oral contraceptives are potential common precipitants, and therefore women requiring hormonal therapy should be carefully managed. Low-dose oral contraceptives and intrauterine devices (IUDs) may be options. Progesterone and progestins should be avoided. Pregnancy raises progesterone levels and carries the risk of exacerbation in women with acute porphyrias. Rather than discouraging pregnancy, these patients should be managed in a specialist center that has experience in dealing with porphyria.

About 10% of patients with acute porphyria have frequent recurrent exacerbations (at least 3-4 per year). Once-weekly hemin infusions can be given as prophylaxis. However, this may necessitate central venous access, and repeated hemin administration can lead to iron overload. Givosiran is a small interfering RNA (siRNA) directed against hepatic ALAS1 and decreases production of ALA. It is given monthly as a subcutaneous injection and has been shown to decrease levels of urinary PBG and

Table 5-7 Supportive measures and monitoring in acute porphyria

Supportive measures
Nutritional support: oral, nasogastric, or intravenous
Pain relief: opiates
Volume depletion: intravenous fluids
Insomnia and restlessness: chloral hydrate or low doses of short-acting benzodiazepines
Nausea and vomiting: chlorpromazine and prochlorperazine
Tachycardia and hypertension: beta blockers with care (hypovolemia)
Seizure prophylaxis, particularly if hyponatremia coexists, and seizure control: gabapentin or vigabatrin; benzodiazepines may be safe
Anesthesia if required: nitrous oxide, ether, halothane, or propofol
Muscle relaxants: suxamethonium
Bladder paresis: catheterization
Monitor
Serum electrolytes, particularly sodium and magnesium
Renal and liver tests
Vital capacity: consider intensive care management if deteriorating
Neurologic status
Bladder distension

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Table 5-8 General and follow-up measures for acute porphyria

Counsel
Alcohol avoidance
Smoking cessation
Information about safe and unsafe medications in porphyria
Avoidance of oral contraceptives
Maintain adequate nutrition
Arrange for medical bracelets
Psychological input for depression
Genetic counseling for families
Photoprotection*
Avoidance of sunlight exposure and skin trauma*
Follow-up
For liver problems, especially chronic liver failure and hepatocellular carcinoma
Those with chronic hypertension require close follow-up
Management of chronic pain
Management of chronic mental health issues

*For porphyrias with cutaneous manifestations only.

ALA levels to normal/near-normal levels. It substantially decreases annualized attack rates and requirements for hemin treatment. Experience with this medication is limited to prevention of frequently recurring attacks. Adverse effects of givosiran included hepatotoxicity, skin rash, nausea, injection-site reaction, decreased glomerular filtration rate, fatigue, and rare anaphylaxis.

Allogeneic liver transplantation has been performed in AIP with success. After transplantation, urinary ALA and PBG levels have returned to normal within 24 h. This, however, should be considered only in those who experience recurrent severe attacks and are unresponsive to other treatments. Gene therapy with adeno-associated virus vector delivering the PBGD gene and enzyme replacement with recombinant human PBGD have been attempted.

Blistering cutaneous porphyrias

These differ from acute porphyrias mainly by the absence of neurological symptoms. It is worth noting that cutaneous manifestations can occur in some AHPs (eg, VP and HCP) as well.

Porphyria cutanea tarda

Porphyria cutanea tarda is the most common human nonacute porphyria. PCT is caused by the inhibition of UROD activity, specifically in the liver, to less than about 20% of normal. It can be classified as either sporadic (type 1) or familial (types 2 and 3). The sporadic form accounts for about 80% of cases. A heterozygous UROD mutation is found in familial type 2 PCT, whereas familial type 3 PCT is hereditary without mutations in UROD and may be due to other shared genetic (eg, HFE mutations) or environmental factors. Clinically, PCT is a heterogenous, iron-related disorder with varying combinations of known susceptibility factors, which may be genetic (UROD or HFE mutations), environmental (smoking, alcohol, and estrogen use), infectious (HCV, HIV), or related to iron overload (HFE mutations, blood transfusions, advance renal disease, etc). Increased iron and CYPs can result in formation of reactive oxygen species that can generate a partially oxidized form of uroporphyrinogen that is a potent inhibitor of hepatic UROD leading to PCT.

PCT usually presents in adults and results from light-induced skin fragility leading to bullous lesions on sun-exposed area of skin, most commonly the dorsum of the hands (Figure 5-10). When blisters rupture, they can cause focal scarring, hypopigmentation and small white papules (milia) are common in the same areas. Hyperpigmentation and increased hair growth can occur particularly on the face, and, occasionally, the skin in sun-exposed areas becomes severely thickened (pseudoscleroderma). Skin symptoms show seasonal variations with more symptoms in the summer and autumn. Like other porphyrias, there is excretion of colored/fluorescent porphyrins in the urine (Figure 5-10). Patients may notice reddish urine due to porphyrinuria. Liver dysfunction is common and can vary from mild impairment to cirrhosis, but advanced cirrhosis is unusual. The incidence of hepatocellular carcinoma is higher in these patients.

Urine and plasma porphyrins are markedly elevated in PCT, with a predominance of uroporphyrin (octacarboxyl porphyrin) and heptacarboxyl porphyrin. Fecal porphyrins may be normal or elevated with increased levels of isocoproporphyrins. Skin biopsy findings are characteristic but not specific, and therefore PCT should be differentiated from other cutaneous blistering porphyrias and acute porphyrias with blistering cutaneous manifestations (VP and HCP). PCT is highly responsive to treatment, but these treatments are specific and not useful in other porphyrias. In addition to avoiding precipitating factors, such as alcohol and iron supplements, phlebotomy to reduce hepatic iron is the preferred treatment at most centers. When using phlebotomy, removal of about 450 mL of blood at 2-wk intervals with a ferritin target of lower limit of normal is reasonable. Plasma porphyrin levels should be followed and will show a gradual decrease because of slow mobilization of porphyrins from the liver. Skin fragility and blistering improve more slowly. Another low-cost and convenient option is low-dose hydroxychloroquine (100 mg twice weekly, which has a better safety profile than chloroquine). This option

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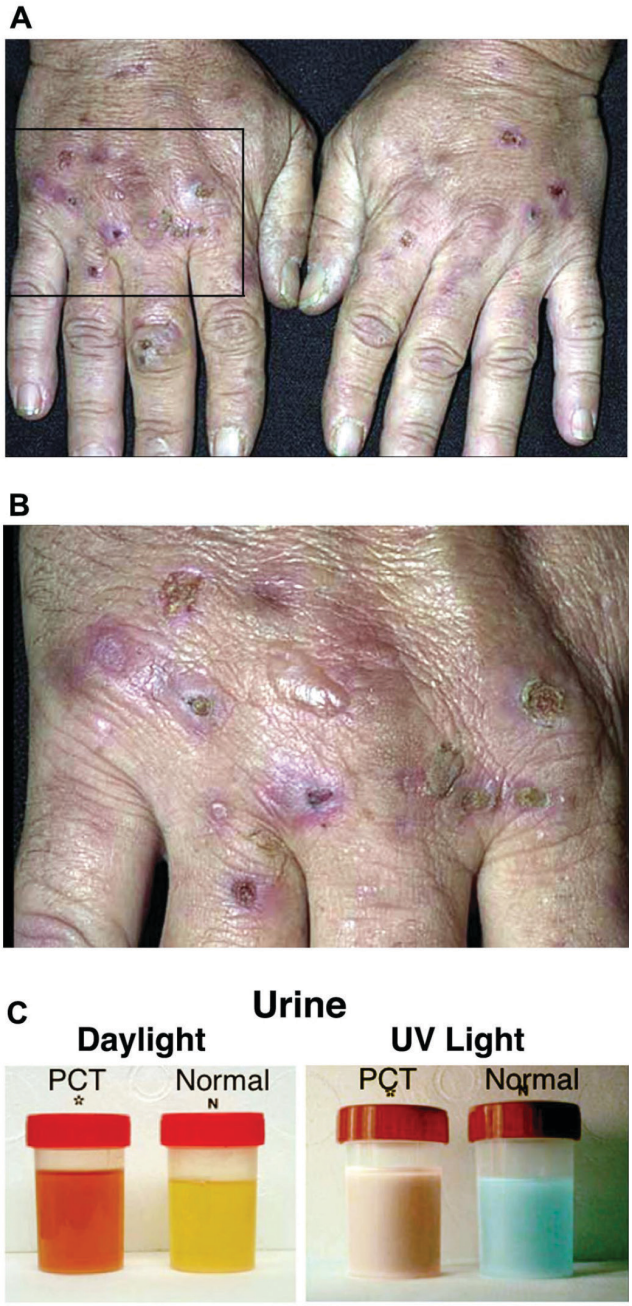

Figure 5-10 Porphyria cutanea tarda results from decreased activity of UROD. (A-B) Sun-exposed hands of a PCT patient showing areas of atrophy and scarring secondary to accumulation of porphyrin precursors and exposure to ultraviolet light. Once the porphyrin precursors absorb light, they emit energy and cause cell damage by peroxidation of lipid membranes, thus disrupting intracellular organelles. (C) Urine from a symptomatic PCT patient and a healthy control in daylight (left) and under ultraviolet light (right). The PCT urine has an orange-red color in daylight that fluoresces red under ultraviolet light. Adapted from Balwani M, Desnick RJ, *Hematology (Am Soc Hematol Educ Program)*. 2012;2012:19-27, with permission.

should be considered in patients with advanced liver disease or heavy alcohol use and can achieve remission as quickly as with phlebotomy. Higher doses of hydroxychloroquine should be avoided in PCT, as it can cause adverse reactions. Iron chelators may be an option if the 2 preferred treatments are not possible. PCT patients with chronic hepatitis C have been shown to achieve PCT remission when treated with antiviral drugs. Treatment of PCT associated with end-stage renal disease (ESRD) is complex, but erythropoiesis-stimulating agents may help with increased iron utilization and hence help with iron reduction.

Pseudoporphyria is a bullous disorder with clinical and histologic features similar to those of PCT but without significant porphyrin elevation. In some cases, a photosensitizing drug is responsible. It originally was observed as skin lesions in patients with renal failure, so-called bullous dermatosis of hemodialysis. Several medications have been associated with pseudoporphyria, including naproxen, nalidixic acid, dapsone, amiodarone, and diuretics. It also may occur in individuals using tanning beds. Clinical features of pseudoporphyria are identical to PCT except that the legs, upper chest, or face may also be involved. In contrast to PCT, however, hypertrichosis and hyperpigmentation usually are not seen. Treatment involves discontinuation of suspected exacerbating factors and sun protection. Hemodialysis-associated pseudoporphyria has been reported to respond to treatment with the antioxidant *N*-acetylcysteine.

Congenital erythropoietic porphyria

Congenital erythropoietic porphyria (CEP), also known as Günther disease, was the first porphyria to be described. It is an autosomal-recessive disorder due to deficient activity of uroporphyrinogen III synthase. Severe blistering cutaneous photosensitivity in CEP usually begins in early infancy. Repeated infections, scarring, hypertrichosis, and bone resorption in CEP can lead to severe disfigurement. Exposure to sunlight in CEP is not associated with pain, and therefore patients are not prompted to avoid sun exposure. Some of the characteristic features include reddish brown teeth (erythrodontia) that fluoresce in ultraviolet light due to excess deposition of porphyrias (Figure 5-11). Corneal scarring and keratitis cause ocular problems. Ineffective erythropoiesis and decreased survival of circulating erythrocytes due to excess porphyrins (mostly uroporphyrin I and coproporphyrin I) in marrow erythroblasts and erythrocytes is a key feature. Severe cases may be transfusion dependent and even present in utero as hydrops fetalis. Mild adult-onset cases have been described with clonal myeloproliferative or myelodysplastic disorders and must be differentiated from PCT by biochemical testing.

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Figure 5-11 Erythrodontia in congenital erythropoietic porphyria, which results from deficient activity of uroporphyrinogen III synthase. Excess porphyrins are deposited in the teeth, which become reddish brown (erythrodontia) and fluoresce in ultraviolet light. Adapted from Balwani M, Desnick RJ, *Hematology (Am Soc Hematol Educ Program)*. 2012;2012:19-27, with permission.

Early diagnosis of CEP is necessary to avoid phototherapy for neonatal jaundice, and red fluorescent urine in diapers is suggestive. Sunlight protection to avoid severe photomutilation and avoidance of skin trauma are also important. Bone marrow transplantation is recommended during early childhood in severe cases. More recently, induction of iron deficiency was shown to improve erythropoiesis and decrease photosensitivity in CEP patients and deserves further study.

Hepatoerythropoietic porphyria

This rare condition is caused by homozygous or compound heterozygous deficiency of uroporphyrinogen decarboxylase. Hepatoerythropoietic porphyria usually presents in infancy or childhood and has clinical characteristics similar to CEP, with red urine, blistering skin lesions, and scarring, and hemolytic anemia and splenomegaly may also develop. Milder adult-onset cases are reported and must be differentiated from PCT. Laboratory findings are similar to PCT except for marked elevation in erythrocyte zinc protoporphyrin. Management and treatment are focused on sunlight avoidance.

Nonblistering cutaneous porphyrias

Protoporphyrias, which include erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP) cause a type of photosensitivity that is different from other cutaneous porphyrias. Patients with protoporphyrias experience pain within minutes of exposure to sunlight, but the skin does not blister or scar. This may be in part because they seek immediate relief from light exposure. These patients are compelled to alter their lifestyles and occupations to accommodate their condition and have been referred to as "shadow jumpers."

Erythropoietic protoporphyria

Erythropoietic protoporphyria, the most common porphyria in children and the third most common in adults (after PCT and AIP), results from mutations in the FECH gene and is inherited in an autosomal-recessive fashion. Loss of function in both alleles of the FECH gene is necessary, as this would result in FECH activity low enough (about 30% of normal) to cause disease. In majority of cases, severe FECH mutation from one parent and a low-expression FECH allele from the other parent results

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in EPP. The low-expression allele, also known as a hypomorphic variant, by itself does not have any clinical significance. This variant is seen in approximately 10% of Caucasians. It is rare in Africans but more common in Japan and China. Excess protoporphyrin accumulation in the bone marrow reticulocytes, circulating erythrocytes, and plasma causes the clinical manifestations in EPP. Protoporphyrins are not soluble in water and therefore rely on biliary excretion and in excess amounts can form gallstones.

In EPP, skin lesions usually begin in early childhood with cutaneous manifestations that are nonblistering compared with the predominantly blistering findings in the other cutaneous porphyrias. A characteristic symptom is a burning sensation within minutes of sun exposure, and if exposure continues, the skin becomes erythematic and swells, and this is followed by systemic symptoms. These lesions rarely vesiculate. Subtle, chronic skin changes may include nail changes and thickening of the skin overlying the knuckles. Some patients may have a mild microcytic, hypochromic anemia with reduced serum ferritin, and this is poorly understood. Late-onset EPP has been described with clonal myeloproliferative disorders and myelodysplastic disorders in association with a heterozygous inherited or somatic FECH mutation. Protoporphyrin in large amounts is cholestatic and may cause severe liver disease. A small population (<5%) of EPP patients may require liver transplantation. Marked elevation of protoporphyrins in erythrocytes is key to the diagnosis of EPP. FECH can chelate iron to the protoporphyrin ring (iron protoporphyrin = heme) as well as zinc. Therefore, when there is a deficiency in FECH, there are increased levels of metal-free protoporphyrins and decreased zinc protoporphyrins. Many laboratories use a hematofluorometer that can measure erythrocyte zinc protoporphyrin levels, but this assay is not useful to diagnose EPP, as it cannot measure metal-free protoporphyrins. Urine porphyrins are not elevated in EPP.

Patients with EPP have a disabling condition, as they are forced to avoid sunlight because of their disease. They often require vitamin D supplementation and require measures to avoid hepatic damage, such as hepatitis A and B vaccination. Sunscreens that block UV light are not effective because wavelengths that excite porphyrins extend into the visible range. Special clothing, opaque sunscreens, and oral beta carotene may be of some benefit. Afamelanotide, an analogue of alpha-melanocyte stimulating hormone that is given as a monthly subcutaneous implant, darkens the skin and can substantially increase sunlight tolerance in EPP. This is particularly useful during summer months. This medication substantially improved quality of life with minimal side effects that included mostly nausea and headache. Although liver transplantation has been attempted in EPP, its success is limited because of continued production of protoporphyrin by the bone marrow. Sequential liver and bone marrow transplantation has also been described. During surgery, modification of lighting is necessary to limit organ injury. Other treatment modalities are in development.

X-linked protoporphyria

X-linked protoporphyria has essentially the same phenotype as EPP but is due to gain-of-function mutations in the *ALAS2* gene. In this condition, there is no ferrochelatase deficiency, and there is excess protoporphyrins in erythrocytes that are mostly metal-free but with a greater proportion of zinc protoporphyrin than in EPP. This contrasts with previously described mutations in the *ALAS2* gene, which are loss-of-function and cause X-linked sideroblastic anemia.

KEY POINTS

- The most common porphyrias: AIP, PCT, and EPP, are distinct disorders with neurovisceral, blistering cutaneous, and nonblistering cutaneous features, respectively. VP and HCP, which are much less common, may have both neurovisceral and blistering cutaneous manifestations.
- AIP and other AHPs are characterized by marked increase in porphyrin precursors ALA and PBG as well as porphyrin intermediates often by several logs.
- Laboratory testing for porphyrias should rely on first-line testing for initial screening and second-line testing only if screening is positive. This allows for cost-effective testing of patients with nonspecific symptoms that suggest porphyrias.
- DNA testing can confirm a diagnosis of porphyria and facilitate screening of family members who may have latent disease.
- The inherited porphyrias are genetically heterogeneous, with many different mutations among different families. PCT, the most common cutaneous porphyria, is primarily acquired, with mutation of the affected enzyme found in only about 20% cases.

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